IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CUBIST PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 12-367 (GMS)
	)	(CONSOLIDATED)
HOSPIRA, INC.,	)	
	)	
Defendant.	)	

PLAINTIFF CUBIST PHARMACEUTICALS, INC.'S
POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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PLAINTIFF'S WITNESSES

Dr. Barry Eisenstein

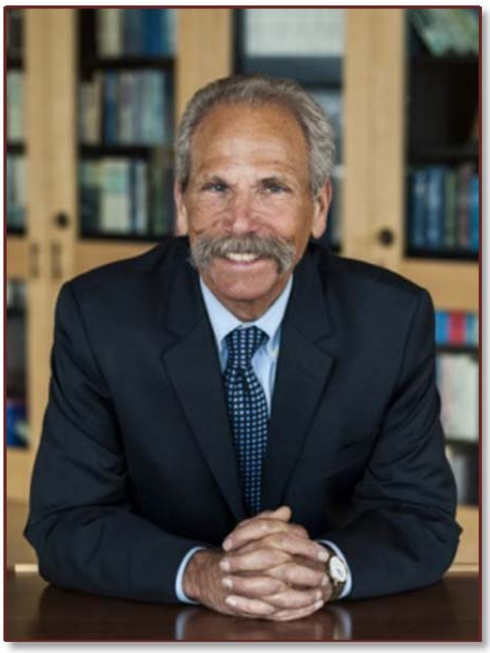
Dr. Eisenstein is currently the Senior Vice President of Scientific Affairs at Cubist. Tr. 624:3-4 (Eisenstein). From 1991-1996, Dr. Eisenstein was Vice President in Lilly Research Laboratories, where his responsibilities included the discovery and development of anti-infective products including daptomycin. Tr. 626:20-627:1, 627:19-628:2 (Eisenstein). He has previously served as a Professor of Medicine at Harvard Medical School and a Professor and Chairman of the Department of Microbiology and Immunology at the University of Michigan Medical School. Tr. 624:23-625:4 (Eisenstein). Dr. Eisenstein testified concerning work on daptomycin at Eli Lilly and Cubist.

Dr. William Gerwick

Dr. Gerwick is a Distinguished Professor of Pharmaceutical Sciences at the University of California, San Diego. Tr. 748:1-5 (Gerwick); PTX-178. He has authored approximately 300 scientific articles, most concerning natural products, and holds over 20 U.S. patents. Tr. 748:24-749:7, 751:7-10 (Gerwick); PTX-178. Dr. Gerwick has worked with around 1,000 natural products during his career, including about 150 lipopeptides. Tr. 748:24-749:7, 749:20-24 (Gerwick).

The Court accepted Dr. Gerwick as an expert in "the purification and structural characterization of natural products." Tr. 752:7-12 (Gerwick). Dr. Gerwick testified about the validity of the '238 and '342 patents, as well as the validity of the RE'071 patent and its Certificate of Correction.

Dr. Joseph Guglielmo



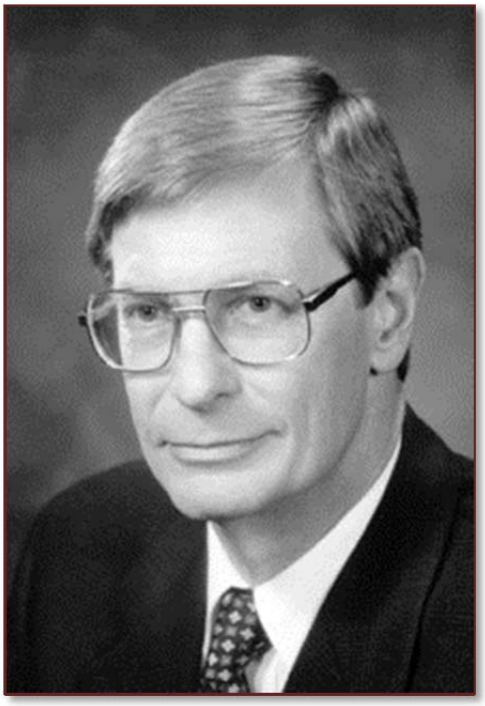
Dr. Guglielmo is the Dean of the School of Pharmacy and the Distinguished Professor in Pharmaceutical Sciences at the University of California, San Francisco. Tr. 940:1-5 (Guglielmo); PTX-179.1. He has been practicing as an infectious-disease-trained pharmacist since the mid-1980s. Tr. 940:15-21 (Guglielmo). Dr. Guglielmo has performed original research and published on the safe and effective use of antibiotics from the 1980s to the present, and is active in teaching about antibiotics and the treatment of infectious diseases. Tr. 940:22-941:22 (Guglielmo); PTX-179.

The Court accepted Dr. Guglielmo as an expert in "pharmacology and the treatment of infectious diseases with antibiotics, including the development of safe and effective methods of administering antibiotics." Tr. 942:13-20 (Guglielmo). Dr. Guglielmo testified concerning the validity of the '967 and '689 patents.

Dr. Thomas Kelleher

Dr. Kelleher is currently the director of process development at Amgen. Tr. 691:1-4 (Kelleher). Prior to that, he was the senior director of manufacturing and process development at Cubist from 1998-2003. Tr. 691:5-15 (Kelleher). Dr. Kelleher is a co-inventor of the '238 and '342 patents. Tr. 690:17-19 (Kelleher); PTX-4; DTX-8. He received a bachelor's degree in biology from the University of Massachusetts and a Ph.D. in industrial and applied microbiology from Rutgers University. Tr. 690:20-23 (Kelleher). Dr. Kelleher testified about the invention claimed in the '238 and '342 patents.

Dr. Robert Moellering



Dr. Moellering, an infectious disease clinician, served as the Chief of Internal Medicine at Deaconess Hospital, Editor in Chief of Antimicrobial Agents and Chemotherapy, and President of the Infectious Diseases Society of America. Tr. 636:11-24 (Eisenstein). He consulted with Eli Lilly on the daptomycin project. Tr. 637:3-7 (Eisenstein). Dr. Moellering testified by deposition concerning this consultation.

Dr. Allan Myerson

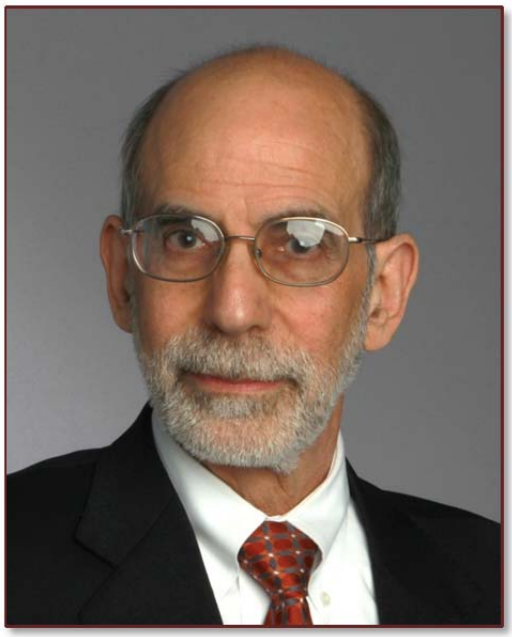
Dr. Myerson is a Professor of the Practice of Chemical Engineering at MIT. Tr. 909:20-23 (Myerson); PTX-180. He is also a principal investigator at the Novartis-MIT Center for Continuous Manufacturing, where his research focuses on separation and purification in pharmaceutical manufacturing processes. Tr. 910:13-23 (Myerson); PTX-180. Dr. Myerson has consulted for a number of pharmaceutical and biotech companies in the area of purification process development. Tr. 911:11-14 (Myerson); PTX-180.

The Court accepted Dr. Myerson as an expert in "the field of separation and purification processes for pharmaceutical products." Tr. 912:9-13 (Myerson). Dr. Myerson testified about objective indicia of non-obviousness for the '238 and '342 patents.

Dr. James Woodworth

Dr. Woodworth, who was employed at Eli Lilly from 1989-2001, was the pharmacokinetic representative to Eli Lilly's daptomycin project team. Tr. 608:8-19 (Woodworth). Dr. Woodworth testified concerning work on daptomycin at Eli Lilly.

Dr. Michael Zeckel



Dr. Zeckel is employed at Eli Lilly and was responsible for the clinical development of daptomycin at Eli Lilly after he joined the company in 1990. Tr. 567:4-5, 568:22-569:3 (Zeckel). Prior to joining Eli Lilly, Dr. Zeckel was an infectious disease physician. Tr. 567:20-21 (Zeckel). Dr. Zeckel testified concerning work on daptomycin at Eli Lilly.

I. INTRODUCTION

1. Plaintiff Cubist Pharmaceuticals, Inc. markets and sells the antibiotic Cubicin® (daptomycin for injection), which is FDA-approved to treat infections caused by certain Gram-positive bacteria. Statement of Uncontested Facts ("UF"), D.I. 109, Ex. 1 ¶¶ C1-C2. Hospira, Inc. filed ANDA No. 202857 and NDA No. 203797 with the FDA seeking approval to manufacture, use, and sell generic versions of Cubicin. UF ¶¶ D1, D5, D7. Cubist alleges that Hospira's proposed generic products would infringe U.S. Patent Nos. 6,468,967 ('967 patent), 6,852,689 ('689 patent), 8,058,238 ('238 patent), 8,129,342 ('342 patent), and RE39,071 (RE'071 patent). UF ¶¶ D4, D6, D10. Hospira has conceded infringement of all asserted claims of all five patents but contests the validity of those asserted claims. UF ¶ E1; D.I. 88.

II. THE ASSERTED CLAIMS OF THE '967 AND '689 PATENTS ARE NOT ANTICIPATED OR OBVIOUS

A. Factual Findings Regarding the Discovery of the Claimed Inventions

1. Others Tried But Failed to Dose Daptomycin Safely and Effectively

2. Gram-positive bacteria, notably methicillin-resistant *Staphylococcus aureus* (MRSA), can cause serious infections of the skin, bloodstream (bacteremia), and heart (endocarditis). Tr. 942:22-949:4 (Guglielmo). This year, MRSA will infect approximately 80,000 Americans and cause 11,000 deaths. Tr. 948:24-949:4 (Guglielmo).

3. Prior to the invention, vancomycin was the only available treatment for serious MRSA infections. Tr. 949:10-15 (Guglielmo). But vancomycin did not work well for all patients, and clinicians worried that MRSA bacteria would eventually develop resistance to vancomycin. *See, e.g.*, Tr. 949:16-950:9 (Guglielmo).

4. In 1983, Eli Lilly began clinical development of daptomycin, a novel antibacterial it had discovered. Tr. 569:6-11 (Zeckel). Lilly, which had significant experience in developing

antibiotics, sought a treatment for Gram-positive infections, including bacteremia and endocarditis due to MRSA, that would be more effective than vancomycin. *See* Tr. 568:10-25, 569:19-570:5 (Zeckel); Tr. 627:2-628:19 (Eisenstein). Lilly's daptomycin project team included chemists, toxicologists, pharmacologists, microbiologists, and clinicians. Tr. 569:6-18 (Zeckel); Tr. 630:16-631:2 (Eisenstein). From 1983 to 1991, Lilly conducted numerous animal studies and nineteen human clinical trials on daptomycin. *See* PTX-195; PTX-185; PTX-186; PTX-182.

5. In Lilly's first Phase II study, daptomycin was administered at 2 mg/kg once a day to patients suffering from a wide variety of infections. Tr. 573:24-575:2 (Zeckel); PTX-185.2.[1] Lilly suspended the study when the drug failed to treat serious infections, such as bacteremia and endocarditis. *See* Tr. 573:24-575:2 (Zeckel); PTX-185.5. In a later Phase II study, Lilly tried to improve efficacy by tripling the daily dose of daptomycin, to 3 mg/kg every 12 hours. Tr. 575:17-576:4, 576:19-577:8 (Zeckel); PTX-186.6. But daptomycin still failed in patients with *S. aureus* endocarditis.[2] Tr. 577:11-22 (Zeckel); PTX-186.32. Lilly thus determined that higher doses of daptomycin would likely be needed to treat serious infections. Tr. 581:17-22 (Zeckel).

6. To test the safety of higher doses, Lilly designed a Phase I "dose escalation" study, in which healthy volunteers would be administered daptomycin at 3 mg/kg every 12 hours, then 4 mg/kg every 12 hours, and finally 5 mg/kg every 12 hours. *See* Tr. 581:23-582:13 (Zeckel); PTX-182.6. The study was abruptly terminated when two of five volunteers receiving 4 mg/kg of daptomycin every 12 hours exhibited muscle weakness and seriously elevated levels of

[1] Page numbers in exhibit citations are to the electronic, or PDF, page of each exhibit.
[2] Hospira has attempted to portray Lilly's Phase II clinical trials as successful, but Dr. Michael Zeckel, a Lilly clinician who worked on the daptomycin project, explained that daptomycin would not be useful to clinicians unless it could treat endocarditis. Tr. 569:1-3, 604:14-606:5 (Zeckel); *see also* Tr. 1098:4-12 (Guglielmo).

creatinine phosphokinase (CPK), an indicator of skeletal muscle toxicity.[3] *See* Tr. 582:14-584:9 (Zeckel); PTX-182.4. Lilly was unable to determine the cause of the CPK elevations. Tr. 583:17-584:15 (Zeckel); Tr. 617:19-618:7 (Woodworth); PTX-183.5.

7. In March 1991, Lilly informed the FDA that it had "voluntarily suspended further evaluation of daptomycin" due to the CPK elevations. Tr. 584:16-23 (Zeckel); PTX-199. In April 1991, the FDA responded by placing all daptomycin studies in humans on clinical hold. Tr. 584:24-585:11 (Zeckel); PTX-200.1.

8. The daptomycin team and other Lilly scientists tried but failed to identify a path forward. Tr. 585:12-586:25 (Zeckel); Tr. 631:17-636:2, 642:22-644:21 (Eisenstein). In particular, they could not determine what was driving the skeletal muscle toxicity or what dose would effectively treat serious infections while avoiding skeletal muscle toxicity. Tr. 586:14-587:16 (Zeckel); Tr. 617:19-618:7 (Woodworth); Tr. 642:22-644:21 (Eisenstein). Lilly also consulted with Dr. Robert Moellering, a professor at Harvard Medical School and a former president of the Infectious Diseases Society of America, who recommended that Lilly stop developing daptomycin because it could not find a safe and effective dosage regimen.[4] *See* Tr. 935:19-936:7 (Moellering); Tr. 636:3-637:12 (Eisenstein).

9. At trial, Dr. Zeckel, Dr. Barry Eisenstein (the head of Lilly's infectious disease program at the time the daptomycin project was terminated), and Dr. James Woodworth (a Lilly pharmacologist working with daptomycin) testified that once-daily dosing of daptomycin to

[3] Although normal CPK levels are 10-120 u/l, the levels observed in the two patients were over 10,000 u/l and 20,000 u/l. Tr. 958:1-12 (Guglielmo); PTX-182.17-18; DTX-14, 2:6-17. Breakdown of skeletal muscle can release myoglobin into the bloodstream, causing kidney failure. Tr. 957:6-25 (Guglielmo).

[4] Hospira's contention that Lilly ceased development of daptomycin for reasons independent of the clinical failures is inconsistent with evidence that Lilly continued to pursue alternatives to vancomycin, initially focusing on analogs of daptomycin and later on the compound oritavancin. Tr. 587:17-588:25 (Zeckel); DTX-268.18.

minimize toxicity was never considered. Tr. 587:1-8 (Zeckel); Tr. 607:20-608:19, 618:13-619:4 (Woodworth); Tr. 626:20-627:1, 644:8-13 (Eisenstein). These witnesses explained that they believed that administering higher doses once-daily would increase toxicity (because more drug would be in the bloodstream at the time of dosing) and reduce efficacy (because lower concentrations of drug would be in the bloodstream at the end of the dosing interval). *Id.*

2. Drs. Tally and Oleson Discovered How to Dose Daptomycin Safely

10. After Cubist acquired rights to develop daptomycin in 1997, Drs. Francis Tally and Frederick Oleson tried to determine what was driving the skeletal muscle toxicity that Lilly observed with daptomycin. *See* DTX-14, 3:63-4:5; Tr. 646:10-12 (Eisenstein); Tr. 143:20-22 (Rausser). They designed dog studies to determine whether the skeletal muscle toxicity was driven by the peak levels of drug in the blood, *i.e.*, $C_{max,}$ or total drug exposure, *i.e.*, AUC.[5] *See* DTX-14, 3:63-4:5; Tr. 966:21-967:3 (Guglielmo). In the first study, one group of dogs received a 75 mg/kg dose of daptomycin once-daily, while a second group received the same total daily dose administered at 25 mg/kg every eight hours. DTX-14 9:28-34; Tr. 967:10-24 (Guglielmo). The results showed that 75 mg/kg once-daily was less toxic than 25 mg/kg every eight hours. DTX-14, 10:17-40; Tr. 968:1-969:20 (Guglielmo). This revealed that toxicity was not primarily driven by C_{max} or AUC; instead, time between doses seemed to play a significant role. DTX-14, 4:22-67, 10:25-52; Tr. 969:21-971:1 (Guglielmo). A second dog study confirmed that skeletal muscle toxicity was driven by dosing frequency rather than C_{max} or AUC. DTX-14.5, 6, 4:22-63, 11:61-12:30; Tr. 972:2-24 (Guglielmo).

11. Drs. Tally and Oleson were the first to determine the relationship between these pharmacokinetic parameters and the skeletal muscle toxicity of daptomycin. Tr. 966:10-13

[5] For a tutorial on these pharmacokinetic parameters, *see* Tr. 959:24-966:9 (Guglielmo); PDX-809-PDX-814.

(Guglielmo); *see also* Tr. 381:20-382:8 (Ebert). Their results were published in the *Journal of Antimicrobial Agents and Chemotherapy*, a premier journal in the field. *See* PTX-290; Tr. 951:1-952:11 (Guglielmo). Subsequent clinical trials further demonstrated the safety and efficacy of once-daily dosing of daptomycin in humans. PTX-33; PTX-47; Tr. 952:12-953:16 (Guglielmo). The results, which were published in prestigious journals including the *Clinical Infectious Diseases* and the *New England Journal of Medicine*, came as a surprise to those in the field. *See* PTX-33; PTX-47; Tr. 951:1-954:4 (Guglielmo); DTX-268. The FDA granted Cubist's NDA for Cubicin priority review. Tr. 649:10-650:2 (Eisenstein).

12. Cubicin is approved for the treatment of complicated skin and skin structure infections, bacteremia, and right-sided endocarditis. UF ¶ C2; PTX-17.2; Tr. 650:9-15 (Eisenstein); *see also* Tr. 1017:3-16 (Guglielmo); Tr. 383:18-384:16 (Ebert). Gross sales of Cubicin have increased every year since its 2003 launch and now total over $3 billion. D.I. 118. U.S. net product revenues in 2013 were $907,978,000. *Id.*

3. The Asserted Claims and the Person of Ordinary Skill in the Art

13. Asserted claims 16, 17, 34, and 35 of the '967 patent are directed to methods of administering therapeutically effective amounts of daptomycin at a dosage interval that minimizes skeletal muscle toxicity. *See* DTX-14, 15:27-43, 15:62-16:5, 16:36-41. Claims 16 and 17 of the '967 patent include the following limitations: (1) administering daptomycin to a "human patient in need thereof"; (2) in a "therapeutically effective amount"; (3) "at a dosage interval that minimizes skeletal muscle toxicity"; (4) wherein the dose is "repeatedly administered;" and (5) "once every 24 hours." *Id.* Claims 16 and 34 specify a dose amount of 4 mg/kg, while claims 17 and 35 require a dose amount of 6 mg/kg. *Id.* Claims 34 and 35 further require that the claimed method "treat[] or eradicat[e] a bacterial infection." *Id.*

14. Asserted claims 51 and 52 of the '689 patent, which are directed to treating renally

impaired patients, claim administration of therapeutically effective amounts of daptomycin at a dosage interval of once every 48 hours in order to minimize skeletal muscle toxicity. *See* DTX-10, 16:38-46, 16:51-54. Claim 51 requires a dose amount of 4 mg/kg, while claim 52 requires a dose amount of 6 mg/kg. *Id*.

15. A person of ordinary skill in the art of the '967 and '689 patents would have been familiar with methods for administering antibiotics. That person would typically hold a degree in pharmacy, medicine, chemistry, biochemistry, physiology, or a complementary discipline relevant to pharmacology, and have experience evaluating information concerning the safety and/or efficacy of drugs in mammals. Tr. 973:17-974:5 (Guglielmo); PDX-817.

B. The Asserted Claims of the '967 Patent Are Not Anticipated

1. Legal Standard for Anticipation

16. Given the statutory presumption of validity, a patent challenger bears the burden of proving each fact underlying its invalidity defenses by clear and convincing evidence. 35 U.S.C. § 282(a); *see Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242-43 (2011). This burden is particularly hard to meet when the prior art upon which the challenger relies was before the Patent Office during prosecution. *See Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012).

17. To demonstrate that the asserted claims of the '967 patent are anticipated, Hospira must present clear and convincing evidence that each and every element of the claims was previously described in a single prior art reference either expressly or inherently, so as to place a person of ordinary skill in possession of the invention. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). Anticipation is a question of fact. *Id*.

2. The Asserted Claims of the '967 Patent Are Not Anticipated by Woodworth

18. Hospira has alleged that Woodworth et al., "Single-Dose Pharmacokinetics and

Antibacterial Activity of Daptomycin, a New Lipopeptide Antibiotic, in Healthy Volunteers," anticipates claims 16, 17, 34, and 35 of the '967 patent. DTX-427. The authors of the Woodworth paper worked at Eli Lilly, and the Woodworth paper was cited to the Patent Office during prosecution of the '967 and '689 patents. DTX-427.1; DTX-14.3; DTX-10.2; Tr. 974:12-14 (Guglielmo).

19. The Woodworth paper describes single-dose studies of daptomycin in healthy volunteers. DTX-427.1; Tr. 974:15-975:3 (Guglielmo). Based on the data from those studies, Woodworth reported on various properties of daptomycin, including protein binding, pharmacokinetics, and antibacterial activity against several strains of bacteria.[6] DTX-427.1-4; Tr. 976:4-10 (Guglielmo). Among other things, Woodworth observed that, due to high protein binding (96.4%), daptomycin may have "limited effectiveness" in treatment of deep-seated infections such as endocarditis. DTX-427.7; Tr. 348:13-24, 351:9-17 (Ebert); Tr. 976:4-10, 981:23-982:13 (Guglielmo).

20. There is no dispute that the actual studies reported in the Woodworth paper do not meet all the limitations of claims 16, 17, 34, and 35 of the '967 patent. Tr. 987:1-11, 988:13-990:1 (Guglielmo); Tr. 343:8-11, 345:3-346:8 (Ebert). Woodworth did not "repeatedly" administer daptomycin to "patients." Nor did he administer daptomycin "until said bacterial infection is treated or eradicated." Tr. 343:8-11, 345:3-15 (Ebert); Tr. 987:1-11, 989:20-990:1 (Guglielmo). Indeed, experts for both parties agreed that administration of a single dose of a drug differs significantly from repeated administration, and single-dose studies may not reveal toxicities that would be associated with repeated dosing. Tr. 975:4-21 (Guglielmo); Tr. 345:7-346:1 (Ebert).

[6] Woodworth measured antibacterial activity by withdrawing blood from the volunteers over a 6-hour period, diluting the blood, and measuring bacterial growth first in a test tube and then in a Petri dish. DTX-427.2; Tr. 978:22-981:22 (Guglielmo); PDX-819-PDX-823.

Woodworth thus did not administer daptomycin in a way that would minimize skeletal muscle toxicity. Tr. 987:1-11 (Guglielmo). Indeed, the Woodworth paper does not mention skeletal muscle toxicity, let alone identify dosage regimens that would minimize skeletal muscle toxicity. Tr. 346:2-8 (Ebert); Tr. 984:16-18 (Guglielmo). Hospira's anticipation defense thus rests not on studies Woodworth actually performed, but on Woodworth's predictions about potential use of daptomycin to treat infection.

(a) Woodworth Would Not Enable a Person of Ordinary Skill to Practice the Invention

21. For Hospira to prevail on its anticipation claim, the Court must find that Woodworth is an enabling reference.[7] That is, the description in Woodworth must be such that a person of ordinary skill in the field of the invention could practice the claimed subject matter based on the reference, without undue experimentation. *Sanofi-Synthelabo*, 550 F.3d at 1085. Whether a prior art reference is enabling presents a question of law based on underlying factual findings. *Impax Labs., Inc. v. Aventis Pharm., Inc.*, 545 F.3d 1312, 1315 (Fed. Cir. 2008). When considering whether a prior art reference requires "undue experimentation," courts look at the reference from the perspective of a person of ordinary skill in the art. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1306-7 (Fed. Cir. 2006). In the case of claims directed to administering pharmaceutical products, mere disclosure of a drug and dose amounts will not necessarily enable a person of ordinary skill to practice the claimed invention without undue experimentation (as Hospira incorrectly suggests). *See, e.g.*, *Impax Labs., Inc.*, 545 F.3d at 1315.

22. The asserted claims of the '967 patent are directed to a method of administering a

[7] Hospira's suggestion that a presumption of enablement applies to non-patent references in district court litigation is not supported by the cases upon which it relies, all of which address prior art publications *during prosecution* or prior art *patents*. *See, e.g.*, *In re Antor Media Corp.*, 689 F.3d 1282, 1289 (Fed. Cir. 2012); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). In any event, in this case there is persuasive evidence of non-enablement. *See infra* ¶¶ 21-31, 44-45.

"therapeutically effective amount of daptomycin . . . at a dosage interval that minimizes skeletal muscle toxicity." DTX-14, 15:29-31. Indeed, the claim term "minimizing skeletal muscle toxicity" was added during prosecution at the urging of the patent examiner, who characterized it as an "essential element" of the invention. PTX-6.141, 151, 161. There is thus no dispute that the claim term "at a dosage interval that minimizes skeletal muscle toxicity" is limiting.[8]

23. Woodworth's predictions on a dose of daptomycin that would be "effective" are speculative at best, given that he did not administer daptomycin to patients, did not administer it repeatedly, and only tested antibacterial activity out to 6 hours in a Petri dish. *See supra* ¶ 19. But even more critically, Woodworth is utterly silent on the essential element of "minimiz[ing] skeletal muscle toxicity."

24. Not surprisingly, Hospira's expert, Dr. Steven Ebert was never asked for and never offered the opinion that, upon reading the Woodworth article, he could practice the claimed invention without undue experimentation. On the contrary, experts for both parties agreed that a person of ordinary skill in the art reading Woodworth would need to conduct additional studies to determine a method for administering daptomycin that would treat infections and minimize skeletal muscle toxicity. *See* Tr. 347:19-348:8, 353:3-7, 380:10-381:3 (Ebert); Tr. 986:21-987:21 (Guglielmo). Indeed, Dr. Ebert candidly admitted that the most one could draw from the last sentence of the abstract in the Woodworth paper (which Hospira focused on at trial) is that some dosing regimen of 4 to 6 mg/kg per day could be tested in clinical trials to treat infections. Tr. 353:3-7 (Ebert). Thus, the dispute is whether the level of experimentation would be "undue."

25. Factors relevant to whether experimentation is undue include the quantity of

[8] Hospira's reliance on cases where claim terms were explicitly found non-limiting is therefore misplaced. *See, e.g.*, *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1377-79 (Fed. Cir. 2001).

experimentation actually needed, the presence or absence of actual examples of the experimental procedure, the amount of guidance provided in the reference, the state of the knowledge already available concerning the subject matter at issue, and the unpredictability of the specific area of science or technology. *Sanofi-Synthelabo*, 550 F.3d at 1085.

26. **The Quantity of Experimentation Actually Needed.** Cubist's expert, Dr. Joseph Guglielmo, testified that designing a dosing regimen is a complicated process requiring consideration of many factors. Tr. 959:14-23 (Guglielmo). "Substantial" experimentation would be needed to progress from the predictions made in the Woodworth paper to the claimed inventions, including additional multiple dose studies in volunteers and clinical studies in patients. Tr. 987:12-21 (Guglielmo). Dr. Ebert agreed that additional human clinical trials would be needed. Tr. 353:3-7 (Ebert). Although Dr. Ebert offered conclusory testimony (not in the specific context of the Woodworth paper) that development of antibiotic dosing regimens through animal models and clinical trials was "routine" as of 1998, he admitted that he has never been involved in the actual design of clinical trials or the development of dosing regimens for unapproved antibiotics. *Compare* Tr. 234:12-21 (Ebert), *with* Tr. 339:15-340:10 (Ebert). And while Dr. Ebert studied daptomycin during the 1980s, he never discovered how to dose daptomycin safely and effectively. *Compare* Tr. 223:15-20 (Ebert), *with* Tr. 341:6-25 (Ebert).

27. Dr. Guglielmo's opinion is supported by evidence of further experimentation that actually occurred. The single-dose studies reported in the Woodworth paper were performed before Dr. Woodworth arrived at Eli Lilly in 1989. Tr. 608:8-9, 610:25-611:4 (Woodworth); DTX-669; PTX-184.3. After that work was completed, Lilly conducted multiple additional human clinical trials. Tr. 576:19-577:8, 581:23-582:13 (Zeckel); PTX-182; PTX-186. Even those additional clinical trials did not enable Lilly to develop a dosage regimen that would

minimize skeletal muscle toxicity. More work had to be done by Drs. Tally and Oleson. *See supra* ¶¶ 10-11.

28. **Presence or Absence of Actual Examples/Amount of Guidance.** The Woodworth paper contains no examples of treatment regimens involving repeated administration of daptomycin to individuals in need of therapy. *See supra* ¶¶ 19-20. Moreover, both Cubist's and Hospira's experts agreed that a person of ordinary skill in the art reading the Woodworth paper would not conclude that a drug with "good antibacterial activity" would necessarily be effective at treating a particular disease. *See* Tr. 348:3-8, 352:25-353:2 (Ebert); Tr. 985:1-12, 1024:5-10 (Guglielmo). Both experts also agreed that Woodworth does not direct a person of ordinary skill in the art to dosing daptomycin once-daily to minimize skeletal muscle toxicity. Tr. 355:18-21 (Ebert); Tr. 1026:23-1027:8 (Guglielmo). Woodworth suggests (at various points) twice-daily, "divided doses," and once-daily (for renally impaired patients). DTX-427.1, 7. As Dr. Ebert explained, the term "divided doses" includes twice-daily, every eight hours, and "you could go on and on, shorter and shorter dosing." Tr. 250:22-251:6 (Ebert). The absence of any guidance toward once-daily dosing is evident insofar as none of the Lilly witnesses who testified at trial, including Dr. Woodworth, ever considered once-daily dosing of daptomycin, let alone at doses of 4 or 6 mg/kg. *See supra* ¶ 9.

29. **State of Knowledge.** At the time of the invention, persons of ordinary skill in the art had concluded that daptomycin was a "dead drug." Tr. 951:18-952:11, 1016:8-15 (Guglielmo); *see also* Tr. 935:19-936:7 (Moellering); Tr. 586:14-587:16 (Zeckel); Tr. 642:22-644:21 (Eisenstein); DTX-268.12, 18; *supra* ¶¶ 4-9.

30. **Unpredictability of the Technology.** Persons of ordinary skill in the art could not predict, based on the Woodworth paper, whether once daily dosing of daptomycin would be

effective in treating infection or minimizing skeletal muscle toxicity as compared to other dosing regimens. As to treating infection, Dr. Ebert conceded that the necessary experiments might or might not produce a response in infections; the studies would have to be conducted to find out. Tr. 353:8-17 (Ebert). And as to minimizing toxicity, Dr. Ebert testified that as of 1998, it was "impossible to tell" whether higher doses or increased frequency of dosing would cause skeletal muscle toxicity. Tr. 380:10-381:3 (Ebert).

31. This case is analogous to others in which courts have held that discussions of proposed future work are not sufficiently enabling to constitute an anticipatory reference. *See, e.g.*, *Apple Inc. v. ITC*, 725 F.3d 1356, 1363-64 (Fed. Cir. 2013); *cf. Forest Labs., Inc. v. Ivax Pharm., Inc.*, 501 F.3d 1263, 1268 (Fed. Cir. 2007).

32. Woodworth would not enable a person of ordinary skill in the art to practice the claimed invention.

(b) Woodworth Does Not Inherently Disclose "Minimizing Skeletal Muscle Toxicity"

33. A critical element of the claimed invention is "minimizing skeletal muscle toxicity." *See supra* ¶¶ 13, 22. Indeed, during prosecution of the '967 patent, the applicants explicitly distinguished Woodworth on the grounds that the reference did not disclose minimizing skeletal muscle toxicity, and the examiner relied upon this distinction in allowing the claims to issue. PTX-7.107-109; PTX-6.173-175, 190.

34. For Hospira to prevail, it must demonstrate by clear and convincing evidence that the limitation "minimizing skeletal muscle toxicity" is inherent in Woodworth. Inherent anticipation requires that the missing descriptive material is necessarily present, not merely probably or possibly present, in the prior art. *See Trintec Indus. v. Top-U.S.A., Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002). Although the Federal Circuit has held that inherent anticipation does not

require that a skilled artisan recognize the inherent characteristic in the prior art,[9] a court should evaluate the opinions of those skilled in the art to determine the scope of the prior art reference. *Glaxo Group Ltd. v. Teva Pharm. USA, Inc.*, C.A. No. 02-219-GMS, 2004 WL 1875017, at *19 (D. Del. Aug. 20, 2004).

35. It is undisputed that Woodworth did not administer daptomycin at 4 or 6 mg/kg once daily and repeatedly to treat infections. *See supra* ¶ 20. Hospira's reliance on cases where the claimed method had been previously practiced is therefore misplaced. *See, e.g.*, *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349-52 (Fed. Cir. 2002); *cf. Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1375, 1378 (Fed. Cir. 2003).

36. Moreover, Dr. Guglielmo testified, in light of the last paragraph of the Woodworth article suggesting administration of 2 or 3 mg/kg every 12 hours, that a person of ordinary skill would construe the last sentence of the Woodworth Abstract as referring to a *total* daily dose of 4 to 6 mg/kg, not once-daily dosing in those amounts. *See* Tr. 984:19-986:6 (Guglielmo).

37. Nor would Woodworth's predicted dosing regimens necessarily minimize skeletal muscle toxicity. On the contrary, both experts agreed that Woodworth suggests dosing regimens that do not minimize skeletal muscle toxicity. *See* Tr. 355:14-17 (Ebert); Tr. 986:14-20 (Guglielmo). For example, Woodworth suggests administering daptomycin in "possibly divided doses" and "every 12 h" in normal patients, and "once- or twice-daily" in renally impaired patients. DTX-427.1, 7.

38. Even Hospira's expert admitted that Woodworth *at most* suggests that some dosing regimen of 4 to 6 mg/kg per day could be tested in clinical trials to treat infections. Tr. 353:3-7

[9] The Federal Circuit's case law holding that a claimed feature can be inherent in the prior art even if not appreciated by persons skilled in the art is seemingly in contradiction with Supreme Court precedent holding the contrary. *See Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45, 66 (1923); *Tilghman v. Proctor*, 102 U.S. 707, 711-12 (1880).

(Ebert). "An invitation to investigate is not an inherent disclosure." *Metabolite Labs, Inc. v. Lab. Corp. of Am.,* 370 F.3d 1354, 1367 (Fed. Cir. 2004). In *Rapoport v. Dement*, the Federal Circuit affirmed a finding that a prior art reference focusing on use of buspirone to treat anxiety, but also mentioning "the possibility of administering buspirone to patients suffering from sleep apnea," did not anticipate claims to using buspirone to treat sleep apnea. 254 F.3d 1053, 1061 (Fed. Cir. 2001). In so holding, the Federal Circuit not only pointed out the "lack of information concerning administration of buspirone to patients while sleeping," *id*., but also rejected an inherency argument on the grounds that "[t]he mere fact that a certain thing *may* result from given set of circumstances is not sufficient." *Id.* at 1063.

39. In short, Federal Circuit cases addressing inherency in the context of products *actually* made or methods *actually* practiced in the prior art do not resolve the issue here: whether, in an unpredictable art, a method can be inherently anticipated by a *prediction* in which persons of ordinary skill in the art would have no reasonable expectation of success. Extending the doctrine of inherency to this type of prediction flies in the face of basic principles of anticipation and obviousness. *See Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1336-37, 1341-42 (Fed. Cir. 2010); *Estee Lauder Inc. v. L'Oreal, S.A.*, 129 F.3d 588, 593 (Fed. Cir. 1997). Innovators who do the hard work of developing safe and effective methods of treatment are entitled to patent their inventions.

40. The limitation "minimizing skeletal muscle toxicity" is not inherent in Woodworth.

3. The Asserted Claims of the '967 Patent Are Not Anticipated by the '226 Patent

41. Hospira has alleged that U.S. Patent No. 5,912,226 ('226 patent), "Anyhydro- and Isomer-A-21978C Cyclic Peptides," anticipates claims 16, 17, 34, and 35 of the '967 patent. The '226 patent, which was cited to the Patent Office during prosecution of the '967 and '689 patents, is generally directed to purified forms of daptomycin and was assigned to Lilly. DTX-

2.2; Tr. 355:24-356:7 (Ebert); Tr. 990:11-13 (Guglielmo).

42. The ’226 patent discloses virtually every possible way to administer daptomycin. DTX-2, 10:19-11:7. For humans, the ’226 patent does not express a preference for any particular dose within the range of 100 mg to 1 gram, let alone single out the claimed 4 mg/kg or 6 mg/kg doses. Tr. 356:20-357:4 (Ebert); DTX-2, 10:57-58. Moreover, a person of ordinary skill in the art would consider both integer and non-integer dose amounts in that range, given daptomycin’s narrow therapeutic window. Tr. 992:5-24 (Guglielmo); *see also* Tr. 357:12-358:5 (Ebert). The ’226 patent also states that daptomycin can be administered as a single daily dose or in multiple doses per day and thus includes essentially every possible interval that a person of ordinary skill in the art would consider. Tr. 991:7-12 (Guglielmo). Even if one were to find clear and convincing evidence that a person of ordinary skill would focus on thirteen dose amounts and five potential dose intervals, the ’226 patent discloses well over 65 potential dose regimens for daptomycin. Tr. 991:16-992:4 (Guglielmo). When one includes non-integer dose amounts, the number of potential dose regimens would be far greater.

43. The ’226 patent does not include information from clinical trials that would be needed to show the association between dose and efficacy. Tr. 359:9-13 (Ebert). Nor does the ’226 patent discuss how to treat any specific infections. Tr. 991:13-15 (Guglielmo).

(a) The ’226 Patent Would Not Enable a Person of Ordinary Skill to Practice the Invention

44. As Dr. Guglielmo explained, a person of ordinary skill in the art would have to do substantial experimentation to get from the ’226 patent’s disclosure to the claimed inventions, including *in vitro* studies, animal models, phase I clinical studies, and ultimately studies in patients with infections. Tr. 994:24-995:13 (Guglielmo). Hospira’s expert provided no evidence to the contrary, but admitted that the ’226 patent does not indicate which dose regimens would

minimize skeletal muscle toxicity and which would not. Tr. 360:24-361:2 (Ebert). The '226 patent does not contain any actual examples or information that would guide a person of ordinary skill in the art to administer daptomycin once daily at 4 or 6 mg/kg. *See supra* ¶ 42. As to the state of the art and the unpredictability of the technology, *see supra* ¶¶ 29-30.

45. The '226 patent would not enable a person of ordinary skill in the art to practice the claimed invention.

(b) The Broad Range of Dosing Regimens Disclosed in the '226 Patent Does Not Anticipate the Claimed Methods

46. It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006); *see also OSRAM Sylvania, Inc. v. Am. Induction Tech., Inc.* 701 F.3d 698, 705-06 (Fed. Cir. 2012).

47. It is undisputed that the '226 patent does not expressly reference skeletal muscle toxicity or disclose how to minimize it. Tr. 359:16-21 (Ebert); Tr. 993:13-15, 993:25-994:12 (Guglielmo). The problem of skeletal muscle toxicity was not even known at the time of the '226 patent. Tr. 360:20-23 (Ebert). The broad disclosure of the '226 patent, which includes at least 65 potential dosing regimens and potentially many more, includes dose regimens that would not minimize skeletal muscle toxicity. Tr. 360:9-19 (Ebert); Tr. 993:16-24 (Guglielmo). The '226 patent does not tell a person of ordinary skill which of the many disclosed dose regimens would minimize skeletal muscle toxicity and which would not. Tr. 360:24-361:2 (Ebert).

4. Ultimate Conclusion on Anticipation

48. Claims 16, 17, 34, and 35 of the '967 patent are not anticipated by Woodworth or the '226 patent.

C. The Asserted Claims of the '967 and '689 Patents Are Not Obvious

1. Legal Standard for Obviousness

49. Obviousness must be demonstrated by clear and convincing evidence that the patented invention would have been obvious to a person of ordinary skill in the art at the time the invention was made. *Eli Lilly*, 619 F.3d at 1336. This determination turns on factual inquiries involving: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1068 (Fed. Cir. 2012). To demonstrate that a patent is obvious in light of a combination of prior art references, the challenger must point to clear and convincing evidence that would motivate a person of ordinary skill in the art to arrive at the inventive result and provide a reasonable expectation of success in doing so. *Eli Lilly*, 619 F.3d at 1336-37; *see also Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1303 (Fed. Cir. 2010).

2. Factual Findings Regarding Non-Obviousness

(a) Scope and Content of the Prior Art

(i) Daptomycin Literature

50. Hospira has alleged that the asserted claims of the ’967 patent are obvious over Woodworth and the ’226 patent in view of the knowledge of one of ordinary skill in the art. This knowledge includes a 1991 abstract by Lee et al., entitled “Abstract 885: Daptomycin versus Conventional Therapy in the Treatment of Endocarditis (E) and Bacteremia” (Lee), and a book chapter by Dr. Richard Baltz, entitled “Lipopeptide Antibiotics Produced by *Streptomyces roseosporus* and *Streptomyces fradiae”* (Baltz). DTX-339.4; DTX-268.3. These references were all cited to the Patent Office during prosecution of the ’967 and ’689 patents. DTX-14.2, 3; DTX-10.2, 3; Tr. 997:6-16, 998:14-999:4 (Guglielmo); Tr. 361:3-7, 364:9-14 (Ebert).

51. At the time of the invention, no dosing regimen had been shown to be safe and effective at treating serious infections. *See supra* ¶¶ 4-9, 29. Neither Woodworth nor the '226 patent disclosed a once-daily dosing regimen that would treat serious infections while minimizing skeletal muscle toxicity. *See supra* ¶¶ 19-20, 33-40, 42-43, 46-47. Woodworth specifically suggests that dosing daptomycin every 12 hours at 2 to 3 mg/kg may produce effective antibacterial activity. DTX-427.7; Tr. 985:19-986:6 (Guglielmo). Moreover, based on a simulation, Woodworth concluded that once-daily dosing would be "unrealistic" because high protein binding of daptomycin in the blood would require very large doses. DTX-427.7; Tr. 982:14-984:15, 1033:19-25 (Guglielmo). Taken as a whole, the Woodworth article thus taught away from once-daily dosing of daptomycin. Tr. 982:14-984:15, 985:19-986:6, 1033:19-25 (Guglielmo).

52. Other daptomycin references upon which Hospira relies suggested that daptomycin could not be used to treat serious infections. For example, Baltz, which summarized the research on daptomycin as of 1997, stated that higher doses would be required to treat endocarditis and other serious infections while also noting that CPK elevations precluded higher doses of daptomycin. The Baltz article concludes that clinical trials were stopped and suggests development of a "daptomycin analog" instead. DTX-268.12, 18; Tr. 999:5-1001:2 (Guglielmo); Tr. 365:16-366:22 (Ebert).

53. The conclusions reached by Baltz are supported by Lee, which describes Lilly's Phase II clinical study where patients were given 3 mg/kg of daptomycin every 12 hours. DTX-339.4. Lee reported that only 2 of 7 patients with *S. aureus* endocarditis had successful outcomes with daptomycin and observed that higher doses may be necessary to treat endocarditis, while also reporting that two patients were discontinued from the study due to elevated CPK levels. DTX-

339.4; Tr. 997:17-998:5 (Guglielmo); Tr. 361:11-14 (Ebert). Lee did not suggest once-daily dosing to either increase efficacy or decrease toxicity. DTX-339.4. Hospira's expert Dr. Ebert acknowledged that Lee does not teach how to minimize skeletal muscle toxicity and only suggests increasing the dosage amount as a way to possibly achieve efficacy. *See* Tr. 361:18-364:8 (Ebert); *see also* Tr. 935:19-936:7 (Moellering).

54. Taken together, Woodworth, the '226 patent, Baltz, and the Lee Abstract would not have motivated a person of ordinary skill in the art to dose daptomycin at 4 or 6 mg/kg once-daily. They offered no suggestion that once-daily dosing of daptomycin would be therapeutically effective or minimize skeletal muscle toxicity. Tr. 1002:1-14 (Guglielmo). In addition, a person of ordinary skill in the art would not have had a reasonable expectation of success that dosing daptomycin once-daily would minimize skeletal muscle toxicity or be therapeutically effective. Tr. 1002:15-1003:2 (Guglielmo). Even Dr. Ebert admitted that a person of ordinary skill in the art would not know that once daily dosing would be effective or minimize skeletal muscle toxicity without testing and that it would be "impossible to tell" whether higher doses would cause skeletal muscle toxicity. Tr. 347:24-348:12, 352:21-353:17, 363:14-364:8, 380:10-381:3 (Ebert).

(ii) Aminoglycoside Literature

55. Hospira has also alleged that the asserted claims of the '967 patent are obvious over Lee and Woodworth in view of literature on dosing of aminoglycosides, another class of antibiotics. References regarding dosing of aminoglycosides were cited to the Patent Office during prosecution, and the specifications of the '967 and '689 patents explicitly reference once-

daily dosing of aminoglycosides. DTX-14, 2:61-3:11; DTX-10 2:63-3:13.[10]

56. Experts for both parties agreed that aminoglycosides differ from daptomycin. Tr. 1003:14-1005:4, 1098:13-1099:9 (Guglielmo); Tr. 367:9-372:13 (Ebert). Aminoglycosides are a completely different class of antibiotics than daptomycin. Tr. 1003:20-25 (Guglielmo); Tr. 368: 17-19 (Ebert). Daptomycin, approved by the FDA in 2003, was the first approved lipopeptide; aminoglycosides have been on the market since the 1950s. Tr. 1004:1-1005:4 (Guglielmo); PDX-830; Tr. 368:9-17 (Ebert). Aminoglycosides and daptomycin have different sites of toxicity: daptomycin is associated with skeletal muscle toxicity, while aminoglycosides are associated with kidney and ear cell toxicity. Tr. 1004:1-1005:4 (Guglielmo); PDX-830; Tr. 369:16-371:5 (Ebert). Further, although daptomycin is highly protein bound, aminoglycosides exhibit low protein binding. Tr. 1004:1-1005:4 (Guglielmo); Tr. 371:16-372:3 (Ebert).

57. A person of ordinary skill in the art would not have looked to aminoglycosides to determine a safe and effective dosing regimen for daptomycin given the differences between the two classes of antibiotics. Tr. 1007:19-1008:12, 1098:13-1099:9 (Guglielmo). There was nothing in the literature concerning aminoglycosides that would have motivated a person of ordinary skill in the art to dose daptomycin at 4 or 6 mg/kg once-daily. Tr. 1006:23-1007:18, 1008:13-1009:2 (Guglielmo). Furthermore, a person of ordinary skill in the art, based on the aminoglycoside literature, would have had no reasonable expectation of success that dosing daptomycin once-daily would minimize skeletal muscle toxicity. Tr. 1009:3-14 (Guglielmo). Taken together, Lee, Woodworth, the state of the art regarding aminoglycosides, and the knowledge of one of ordinary skill in art did not teach once-daily dosing of daptomycin to

[10] The specific aminoglycoside references referenced by Hospira at trial include: DTX-312; DTX-270; DTX-290; and DTX-305. DTX-312, DTX-290, DTX-270 were before the Patent Office during prosecution. DTX-10.5-6; DTX-14, 2:65-66.

minimize skeletal muscle toxicity.

(iii) Renal Impairment Literature

58. Hospira also alleges that the asserted claims of the '689 patent are obvious over Woodworth, the '226 Patent, and the art concerning administration of antibiotics to renally impaired patients.[11]

59. At the time of the invention, the general approach to dosing a drug in renally impaired patients was to either reduce the individual dose of the drug or extend the interval between doses, or combine dose reduction and interval extension. Tr. 1010:2-9 (Guglielmo). However, these approaches assume knowledge of the proper dosage regimen for a person with normal kidney function. Tr. 1010:10-19 (Guglielmo).

60. The general approaches to dosing for renal impairment would not have assisted a person of ordinary skill in the art in dosing daptomycin because there was no known daptomycin dosage regimen for patients with normal kidney function. Tr. 1010:10-19, 1012:11-24 (Guglielmo). As of 1998, it was "impossible to tell" the proper dosing regimen for daptomycin. Tr. 380:14-381:3 (Ebert); Tr. 1010:10-19 (Guglielmo). There was nothing in the prior art that would have motivated a person of ordinary skill in the art to dose daptomycin at 4 or 6 mg/kg once every 48 hours. Tr. 1012:25-1013:4 (Guglielmo). In addition, a person of ordinary skill in the art would not have had a reasonable expectation that dosing daptomycin at 4 or 6 mg/kg once every 48 hours in renally impaired patients would have minimized skeletal muscle toxicity. Tr. 1013:5-10 (Guglielmo). Taken together with the daptomycin and aminoglycoside references, the literature on renal impairment did not teach extending the dosing interval for daptomycin to once every 48 hours to minimize skeletal muscle toxicity in renally impaired patients.

[11] The specific renal impairment references mentioned at trial include: DTX-312; DTX-355; DTX-371; and DTX-392. DTX-312 and DTX-392 were before the Patent Office during prosecution. DTX-10.3, 6; DTX-14.3.

(iv) Other Drugs

61. Hospira has asserted, based on art concerning amphipathic drugs, that a person of skill in the art would have known that skeletal muscle toxicity was reversible and that reversible toxicities could be minimized by extending the dosing interval. The drugs upon which Hospira relies are very different from daptomycin. *See* Tr. 373:12-374:24 (Ebert). A person of skill in the art would not have considered them when trying to determine a dosing regimen for daptomycin. Tr. 1013:17-1015:5 (Guglielmo).

(b) Objective Indicia of Non-Obviousness

62. At the time of the invention in the late 1990s, there was a need for new antibiotics to treat serious MRSA infections and, more specifically, a need for a safe way to dose daptomycin at levels needed to treat serious infections. *See supra* ¶¶ 2-3. Others in the field, including experts at Lilly and its consultants, were unable to develop a daptomycin dosing regimen that was shown to be both safe and effective and never considered once-daily dosing at 4 or 6 mg/kg. *See supra* ¶¶ 4-9. Indeed, persons of skill in the art were surprised when Drs. Tally and Oleson discovered that dosing daptomycin once a day at 4 or 6 mg/kg provided a safe and effective dose. *See supra* ¶ 11. And once Cubist discovered how to administer daptomycin safely to treat serious infections, daptomycin became a clinical and commercial success.[12] *See supra* ¶ 12.

3. Proposed Conclusions of Law Regarding Non-Obviousness

63. Hospira has failed to prove by clear and convincing evidence that the asserted claims of the '967 and '689 patents would have been obvious to one of ordinary skill in the art at the time of the invention in view of the prior art. *Eli Lilly*, 619 F.3d at 1336. Objective indicia of non-obviousness, including long-felt but unmet need, failures of others, unexpected results, and

[12] There is a clear nexus between Cubicin's commercial success and the asserted claims of the '967 and '689 patents, which cover Cubicin's FDA-approved dosing regimen. Tr. 1154:13-1157:8 (Rausser).

commercial success show that the inventions claimed in the '967 and '689 patents were not obvious. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007).

III. THE ASSERTED CLAIMS OF THE '238 AND '342 PATENTS ARE NOT ANTICIPATED OR OBVIOUS

A. Factual Findings Regarding the Discovery of the Claimed Inventions

1. Impurities Produced During Fermentation of Daptomycin Must Be Removed

64. Daptomycin is obtained by fermenting the soil microorganism *Streptomyces roseosporus* (*S. roseosporus*).[13] PTX-4, 1:58-63; Tr. 758:6-14 (Gerwick). The fermentation is done in large vats, which contain around 20 tons of cells in a "thick broth . . . [with] the consistency of pea soup." Tr. 694:13-15 (Kelleher). The fermentation of *S. roseosporus* produces a complex mixture containing "hundreds to thousands of compounds" and small amounts of daptomycin. Tr. 759:23-760:6 (Gerwick). Isolating the daptomycin from other compounds is very difficult. *Id.*

65. Three types of compounds other than daptomycin can be found in the fermentation mixture: endotoxins, saponins, and a group of daptomycin related substances identified in Table 3 of the '238 and '342 patents. *See, e.g.*, Tr. 696:9-14 (Kelleher); PTX-4, 33:63-34:19. The amounts of these substances must be tightly controlled in a daptomycin drug substance. *See* Tr. 760:1-4 (Gerwick). Endotoxins, are "very bad for human health" and—in even small amounts—can cause fevers in humans. Tr. 469:7-20, 510:1-17 (Baker). As a result, the FDA regulates the amount of endotoxins that can be present in pharmaceutical compositions. Tr. 509:20-25 (Baker). Similarly, saponins are believed to be biologically active in humans and are generally removed from pharmaceutical compositions. Tr. 529:22-530:9 (Baker). Saponins also interfere with the operation of certain purification processes. Tr. 530:10-16 (Baker); DTX-12, 2:11-16.

[13] Fermentation involves introducing a microorganism into a mixture of water and nutrients, on which the microorganism feeds. Tr. 758:15-21 (Gerwick).

At least two daptomycin related substances are known to have biological activity, making them undesirable in pharmaceutical compositions. PTX-3, 7:67-8:2; Tr. 696:21-697:1 (Kelleher).

2. Cubist's Initial Attempts to Purify Daptomycin

66. After in-licensing daptomycin from Lilly, Cubist began to produce daptomycin for use in clinical trials. Tr. 692:6-11 (Kelleher). Cubist, like Lilly, produced daptomycin through fermentation. Tr. 693:15-694:10 (Kelleher). To isolate daptomycin from the fermentation broth, Cubist used a modified version of the process described in Lilly's investigational new drug application. Tr. 695:23-696:2 (Kelleher); DTX-79.118. This process used multiple rounds of hydrophobic interaction chromatography,[14] which separates molecules based on their "relative oiliness." Tr. 699:4-8 (Kelleher); PTX-29.1.

67. Cubist soon experienced two serious problems with this process. First, the process did not consistently remove endotoxins and saponins, and produced daptomycin with relatively high amounts of daptomycin related substances. Tr. 696:9-14 (Kelleher). The failure to remove endotoxins was particularly serious because the resulting batches were unsuitable for use in humans. Tr. 706:12-18 (Kelleher). Second, because the process could only recover about 2-5% of the daptomycin created by fermentation, it was not commercially viable. Tr. 696:9-10, 693:7-14, 715:16-21 (Kelleher); Tr. 916:11-24 (Myerson). Cubist scientists thus set out to develop a new manufacturing process that would produce commercially viable amounts of daptomycin with clinically acceptable levels of endotoxins, saponins, and daptomycin related substances. Tr. 696:6-13 (Kelleher).

3. The Inventions of the '238 and '342 Patents

68. Cubist's top priority was to remove endotoxins. Tr. 706:12-18 (Kelleher). To do this,

[14] Hydrophobic interaction chromatography separates daptomycin from its impurities based on how much those impurities associate with themselves instead of water. The more "water hating" a molecule is, the more "hydrophobic" it is. *See* Tr. 412:2-412:7, 546:11-13 (Baker).

Cubist scientists first tried using "ultrafiltration." Tr. 706:19-22 (Kelleher). Ultrafiltration involves passing a mixture through a filter with very small holes; molecules larger than the holes are retained on the ultrafilter, while molecules smaller than the holes pass through. Tr. 711:17-23 (Kelleher). Because endotoxins are generally larger than daptomycin, Cubist scientists believed that ultrafiltration (with an appropriate hole size) would retain endotoxins but allow daptomycin to pass through. Tr. 706:21-707:5 (Kelleher). This, they thought, could remove the harmful endotoxins from Cubist's first daptomycin batch. *Id.* Surprisingly, the daptomycin did not pass through the ultrafilter. *Id*. For the next three or four months, Cubist scientists tried to determine why this experiment failed. Tr. 707:8-23 (Kelleher). They determined that the daptomycin molecules had combined, or "aggregated," to form a "micelle," a structure several times larger than a single molecule of daptomycin. *Id.* Daptomycin micelles were too large to fit through the holes in the ultrafilter, so they were retained on it. *Id.* In the course of this investigation, Cubist scientists made another surprising discovery. Daptomycin formed micelles at acidic pH, but, unexpectedly, these micelles broke apart into individual daptomycin molecules at neutral pH. *Id.* Cubist thus discovered that daptomycin's ability to form micelles is reversible. *Id.*

69. Dr. Thomas Kelleher, then head of process development at Cubist, realized that daptomycin's ability to reversibly form micelles could be used to improve the daptomycin purification process. Tr. 691:6-9, 708:6-14 (Kelleher). First, the daptomycin fermentation mixture could be ultrafiltered at acidic pH. Tr. 711:17-712:13 (Kelleher). Small impurities, like saponins, would pass through the ultrafilter and be removed, while daptomycin micelles would be retained on the ultrafilter (along with large impurities). *Id.* Then, the pH could be raised to neutral to break up the micelles. *Id.* This time, the individual daptomycin molecules would pass

through the ultrafilter, while the larger impurities, such as endotoxins, would be retained on it. *Id.* Using both steps, large and small impurities could be separated from daptomycin. *See, e.g.*, PTX-4, 20:26-21:6.

70. Dr. Kelleher, together with the other inventors, then set out to develop a method to increase the purity of daptomycin relative to the daptomycin related substances. When Dr. Kelleher and the other inventors began their work, scientists widely believed that there was an upper limit on the purity of daptomycin that could be achieved. Tr. 703:8-705:7 (Kelleher); DTX-146.95. In particular, scientists at Lilly and Cubist believed that as certain daptomycin-related impurities were removed, daptomycin itself would naturally break down to form more of those impurities. Tr. 702:17-23 (Kelleher); DTX-146.95. However, over a period of 18 months, the inventors devised a method using anion exchange chromatography that could consistently produce daptomycin compositions of greater than 93% purity, and in some cases up to 99% purity, when used under specific conditions. Tr. 699:15-700:20, 702:6-13, 703:10-13 (Kelleher); PTX-4, 4:4-6, 5:37-45, 12:54-65, 14:8-20, 31:60-32:14. These compositions had minimal levels of daptomycin related substances and other impurities.

71. The overall process that Cubist developed produces daptomycin with very low levels of endotoxins, almost no saponins, and low levels of daptomycin related substances. Tr. 715:22-716:12 (Kelleher). The process also delivers yields of 25-35%, which enables commercial production of daptomycin. *Id*. Cubist uses these discoveries, which are described and claimed in the ’238 and ’342 patents, in its commercial process. *See* PTX-29.8; Tr. 713:3-10 (Kelleher).

4. The Asserted Claims and the Person of Ordinary Skill in the Art

72. The ’238 and ’342 patents are both entitled “High Purity Lipopeptides.” PTX-4; DTX-8; UF ¶¶ B3-B4. Asserted claims 91, 98, and 187 of the ’238 patent and 23 and 53 of the ’342 patent are all product-by-process claims directed to high purity daptomycin compositions made

by processes that use micelles or aggregates.

73. A person of ordinary skill in the art of the '238 and '342 patents at the time of the inventions would have had a degree in chemistry, biochemistry, chemical engineering, or a complementary discipline, and laboratory experience in the manufacturing, purification, analysis, and/or characterization of pharmaceutical products for medicinal use. Tr. 774:7-16 (Gerwick).

B. Claim 98 of the '238 Patent Is Not Anticipated by Lilly's '843 Patent

1. Legal Standard for Anticipation

74. "[A] product-by-process claim can be anticipated by a prior art product that does not adhere to the claim's process limitation" if the prior art product is the same as the claimed product. *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1370 (Fed. Cir. 2009). However, if the process limitations of the product-by-process claim impart "structural and functional differences" from the prior art in the claimed product, then the prior art product is not the same as the claimed product and the claim is not anticipated. *Id.* The structural and functional differences that distinguish the claimed product from the prior art product do not need to be expressly recited in the claim, as long as they are inherently included in the claim by virtue of the process limitations. *Id.* The party alleging anticipation of a product-by-process claim bears the burden of showing that the prior art product is the same as the claimed product, *id.*, as Hospira has conceded, Tr. 423:18-424:11 (Hospira Counsel).

2. Claim 98 of the '238 Patent Is Not Anticipated

75. Claim 98 of the '238 patent claims "[a] purified daptomycin composition comprising daptomycin of greater than or about 93% purity" relative to the daptomycin related substances and made using particular method steps. *See* PTX-4, 40:34-38, 43:7-30. Significantly, the claimed product is a composition that includes both daptomycin and other substances. Tr. 505:2-9 (Baker). As Hospira's expert acknowledged, the constituents of the composition as a whole

are important to determining the composition's properties and potential uses. Tr. 505:10-24 (Baker). For example, a composition that is 90% daptomycin and 10% water would be a better drug product than a composition that is 99% daptomycin and 1% cyanide. *Id.*

76. Claim 98 does not expressly recite upper limits for any impurities beyond the daptomycin related substances. *See* Tr. 529:5-7 (Baker). Claim 98 does, however, recite process limitations that reduce the levels of other impurities and therefore inherently define the claimed daptomycin composition. These process limitations include formation of a daptomycin aggregate, separating the aggregate from low molecular weight contaminants, changing the daptomycin aggregate into individual daptomycin molecules, and separating the individual daptomycin molecules from high molecular weight contaminants. *See* PTX-4, 43:7-30.

77. First, the process limitation in claim 98 requiring "separating the daptomycin monomers . . . from high molecular weight contaminants" "by a size selection technique" such as "ultrafiltration," produces daptomycin compositions that contain minimal levels of endotoxins. PTX-4, 43:23-30. Example 15 of the '238 patent describes a daptomycin composition with "measurable pyrogen" being purified by ultrafiltration under conditions in which daptomycin is in monomer form (*i.e.*, neutral pH), in accordance with a process limitation of claim 98. DTX-3, 36:46-47, Tr. 513:7-12, 515:17-516:25 (Baker); 778:4-779:4 (Gerwick); *supra* ¶ 76. In the resulting daptomycin composition, "pyrogen content is reduced to undetectable levels." DTX-3, 36:52-56; *see also* Tr. 514:24-515:4 (Baker); 778:18-779:4 (Gerwick).

78. Second, this same process limitation in claim 98 also removes certain of the daptomycin related substances from the resulting daptomycin compositions. Tr. 787:4-11 (Gerwick). As described in Example 15, in compositions that result from the ultrafiltration step at neutral pH, "several impurities that had been present at 0.1-0.2% are removed." PTX-4,

36:52-56; *see also* Tr. 517:11-16 (Baker); Tr. 787:4-11 (Gerwick). This reduction in the number of daptomycin related substances is consistent with the results of the Cubist commercial process, which is an embodiment of claim 98 of the '238 patent. Tr. 782:14-16 (Gerwick).

79. Third, the process limitation in claim 98 requiring "separating the daptomycin aggregate from low molecular weight contaminants" "by a size selection technique" such as "ultrafiltration," PTX-4, 43:9-22, produces daptomycin compositions that contain minimal levels of saponins. Tr. 781:24-783:2 (Gerwick). As Cubist's expert, Dr. Gerwick, testified, any saponins in the daptomycin fermentation products are removed by ultrafiltration of daptomycin micelles. *Id.* Dr. Baker, Hospira's expert, testified that he had "no reason to disagree" with Dr. Gerwick's analysis concerning the removal of saponins in the '238 patent. Tr. 533:8-14 (Baker). Moreover, the reduced saponin content of the daptomycin compositions of claim 98 is consistent with the results of the Cubist commercial process, which is an embodiment of the claim. *See supra* ¶ 78; Tr. 782:14-16 (Gerwick). Saponins are not present in the compositions produced by the Cubist commercial process. Tr. 717:16-718:5 (Kelleher); DTX-127.12.

(a) The Claimed Daptomycin Compositions Differ from the Compositions Produced by the Method of Lilly's '843 Patent

80. Hospira asserts that U.S. Patent No. 4,874,843 ('843 patent) anticipates claim 98. Tr. 503:11-13, 507:16-19 (Baker). The '843 patent discloses a method of purifying daptomycin that was developed by scientists at Lilly in the 1980s. *See* Tr. 413:18-414:12 (Baker). The patent describes a method for producing daptomycin compositions having, at best, about 93% purity. *See* Tr. 414:16-23 (Baker). The Patent Office considered the '843 patent during prosecution of the '238 patent. *See* PTX-4; Tr. 510:25-511:3 (Baker). The specification of the '238 patent also discusses the '843 patent extensively. *See, e.g.*, PTX-4, 2:39-64.

81. The daptomycin compositions produced by Lilly's '843 patent process are structurally

and functionally different from the daptomycin compositions of claim 98 of the '238 patent in three key ways. *See* Tr. 776:18-777:7 (Gerwick). First, compositions produced by Lilly's '843 patent process contain higher levels of endotoxins than the compositions of claim 98. Tr. 519:20-520:1 (Baker); Tr. 779:5-17 (Gerwick). Daptomycin compositions produced by Lilly's '843 patent process generally contain endotoxins. Tr. 777:22-778:17 (Gerwick). By contrast, daptomycin compositions produced in accordance with claim 98 have reduced levels of endotoxins. *See supra* ¶ 77. As explained above, this difference is expressly demonstrated in Example 15 of the '238 patent. *Id.* The lower levels of endotoxins in the compositions of claim 98 render those compositions structurally and functionally different from the compositions produced by Lilly's '843 patent process. Tr. 776:18-779:17, 842:19-843:6 (Gerwick). Indeed, there is no dispute that daptomycin compositions containing endotoxins are "very different" from daptomycin compositions that do not contain endotoxins. Tr. 513:18-514:1 (Baker).

82. Second, compositions produced by Lilly's '843 patent process contain higher levels and greater numbers of the daptomycin related substances than the compositions of claim 98. Example 10 of the '238 patent recreates the material produced by Lilly's '843 patent process and reports its impurity profile, concluding that the product of Lilly's '843 patent process has fourteen daptomycin related substance impurities. Tr. 534:15-536:16 (Baker); Tr. 783:18-784:23 (Gerwick); PTX-4, 21:59-67, 33:58-35:3. Example 15 of the '238 patent demonstrates that the process steps in claim 98 remove several of these impurities from the claimed daptomycin compositions. *See supra* ¶ 78. The absence of some daptomycin related substances is a structural and functional difference between the compositions of claim 98 and the compositions produced by Lilly's '843 patent process. Tr. 842:19-843:6 (Gerwick).

83. Third, compositions produced by Lilly's '843 patent process contain higher levels of

saponins than the compositions of claim 98. Tr. 781:14-23 (Gerwick). There is no dispute that saponins are present in daptomycin compositions produced according to Lilly's '843 patent process. *Id.*; Tr. 532:19-533:2 (Baker). By contrast, daptomycin compositions produced in accordance with claim 98 have lower levels of saponins. *See supra* ¶ 79. The low levels of saponins in the compositions of claim 98 render those compositions structurally and functionally different from the compositions produced by Lilly's '843 patent process. Tr. 776:18-777:7 (Gerwick). First, because saponins are suspected to be biologically active in humans, Tr. 529:22-530:9 (Baker), the compositions of claim 98 behave more predictably and are safer than the compositions produced by Lilly's '843 patent process. *See* Tr. 779:12-17 (Gerwick); Tr. 709:24-710:6 (Kelleher). Second, because saponins interfere with downstream purification steps and affect yield, *see* Tr. 530:10-12 (Baker); DTX-12, 2:11-31, the compositions of claim 98 are produced in higher yields. The ability to produce an active pharmaceutical ingredient in higher yield affects whether the drug can be commercialized. *See, e.g.*, Tr. 925:23-921:4 (Myerson).

(b) Hospira Presented No Evidence That Lilly's Daptomycin Batches Were Made by Lilly's '843 Patent Process

84. Hospira contended at trial that certain documents showing the purity of daptomycin batches produced by Eli Lilly in the late 1980s and early 1990s establish that Lilly's '843 patent process produced daptomycin that is the same as the compositions of claim 98. *See, e.g.*, Tr. 57:21-58:5 (Hospira Opening). Specifically, Hospira relied on a section from Cubist's NDA submission for daptomycin showing purity levels for Lilly compositions (DTX-79.124-126), a Jan. 30, 1986 Lilly document describing three batches of daptomycin (DTX-116), and a Dec. 1, 1987 Lilly document describing six batches of daptomycin (DTX-186).

85. None of these documents (or any other documents or testimony presented by Hospira) demonstrate that Lilly's '843 patent process produces daptomycin compositions identical to the

claimed compositions. First, there is no evidence establishing that the daptomycin compositions described in the documents Hospira relies on were made by Lilly's '843 patent process. Hospira neither offered nor elicited testimony establishing the method used to make these compositions. *See* Tr. 423:7-20, 475:2-5 (Baker); Tr. 725:22-726:4, 746:13-18 (Kelleher); Tr. 897:20-898:20 (Gerwick). Moreover, the documents themselves cast doubt on any inference that the compositions were produced by Lilly's '843 patent process. The NDA excerpt expressly says "[c]omparison to the Lilly [process] is not possible due to the sparse process history available," DTX-79.127; Tr. 897:20-898:20 (Gerwick), and the January 1986 document was prepared nearly two years before the priority date of Lilly's '843 patent. DTX-116.

86. Furthermore, none of these documents establish that the batches they describe are the same as the claimed compositions. None of the documents include data on the saponin content or specific amounts of daptomycin related substances in the batches. The NDA excerpt expressly says that the purity numbers reported are measured relative to "*total* related substances," without stating how much of each related substance is present. DTX-79.126 (emphasis added); Tr. 426:4-6 (Baker). Moreover, it does not provide information regarding the endotoxin or saponin content of the batches. *Id.* Similarly, the Lilly documents contain no information about saponin content or the amounts of individual daptomycin related substances. DTX-116; DTX-186.

87. The documents on which Hospira relies provide incomplete information regarding daptomycin compositions that have not been linked to Lilly's '843 patent. Accordingly, Hospira has failed to prove by clear and convincing evidence that the product of claim 98 of the '238 patent is the same as the product produced by Lilly's '843 patent.

3. Ultimate Conclusion on Anticipation

88. Claim 98 of the '238 patent is not anticipated by the '843 patent.

C. The Asserted Claims of the '238 and '342 Patents Are Not Obvious

1. Legal Standard for Obviousness

89. The general framework for a non-obviousness analysis is described above. *See supra* ¶ 49. A product-by-process claim is invalid if a product made by the process recited in the product-by-process claim is obvious from prior art products, even if those prior art products are made by different processes. *See Amgen*, 580 F.3d at 1370 n.14. However, if the claimed product is not the same as prior art products as a result of the process limitations (*i.e.*, if the claimed product is structurally and functionally different from prior art products), the claimed product may be non-obvious over prior art products. *See id.* at 1370.

90. A product in a more pure form is non-obvious if the prior art recognized its valuable qualities in purer form but did not disclose any means of producing such purity. *See Application of Irani*, 427 F.2d 806, 809 (C.C.P.A. 1970); *Application of Cofer*, 354 F.2d 664, 667-68 (C.C.P.A. 1966). Factors that must be considered in determining whether a claimed composition is non-obvious include whether the claimed composition has different uses from the prior art compositions, as well as "whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form." *Cofer*, 354 F.2d at 667-68. "[T]he absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds." *Application of Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968); *see also Application of Grose*, 592 F.2d 1161, 1168 (C.C.P.A. 1979).

2. Factual Findings Regarding Non-Obviousness

(a) Scope and Content of the Prior Art

91. Hospira contends that the key prior art references for the '238 and '342 patents are:

Lilly's '843 patent; the book "Protein Purification: Principles, High Resolution Methods, and Applications," (J. Janson & L. Ryden eds., 1998) (DTX-385) ("Protein Purification"); an article authored by Debono in 1987, M. Debono et al., *A21978C, A Complex of New Acidic Peptide Antibiotics: Isolation, Chemistry, and Mass Spectral Structure Elucidation*, 40 J. Antibiotics 761 (1987) (DTX-292) ("Debono 1987"); an article by Lin, S.-C. Lin & H.-J. Jiang, *Recovery and Purification of the Lipopeptide Biosurfactant of* Bacillus subtilis *by Ultrafiltration*, 11 Biotech. Techniques 413 (1997) (DTX-345) ("Lin"); and an article by Lakey, J. Lakey & M. Ptak, *Fluorescence Indicates a Calcium-Dependent Interaction Between the Lipopeptide Antibiotic LY146032 and Phospholipid Membranes*, 27 Biochemistry 4639 (1998) (DTX-333) ("Lakey").

92. Lilly's '843 patent teaches a method for the purification of daptomycin compositions providing at best about 93% purity relative to impurities 1-14. *See supra* ¶ 80. As explained above, compositions prepared according to the method of Lilly's '843 patent contain endotoxins, saponins, and fourteen daptomycin related substances. *Id.* The amount of each of the daptomycin related substances produced by Lilly's '843 patent process is shown in Table 3 of the '238 and '342 patents. PTX-4, 34:1-20; DTX-8, 33:56-34:13; Tr. 535:18-536:16 (Baker). As Hospira concedes, in the product of Lilly's '843 patent, six of the fourteen daptomycin related substance impurities are present in amounts greater than 0.5%. Tr. 539:8-15, 542:22-543:2 (Baker).

93. Lilly's '843 patent further teaches that purifying daptomycin is difficult:

> Final resolution and separation of [daptomycin] from structurally similar compounds is impeded by the presence of impurities which are not identifiable by ultraviolet analysis of the fermentation broth. These so-called "non-uv" impurities are primarily saponins and other fragments. These compounds have solubility characteristics similar to [daptomycin] and are difficult to separate from [daptomycin]. The presence of these compounds causes foaming during concentration procedures and poor resolution during subsequent chromatographic separation steps.

DTX-12, 2:11-22. Lilly's '843 patent then goes on to explain that many purification methods were not effective for purifying daptomycin: "[a]ttempts to remove these impurities by various chromatographic methods, including reverse-phase chromatography on silica gel/C18 (Quantum LP-1), normal phase chromatography over silica gel, and ion-exchange chromatography, failed to significantly improve the purity of [daptomycin]." *Id.* at 2:23-28. These methods were "plagued by low capacity, poor resolution and low recovery of [daptomycin]." *Id.* at 2:29-31. Lilly's '843 patent did not discuss, expressly or inherently, the formation of daptomycin micelles. Tr. 553:23-554:1 (Baker).

94. A person of ordinary skill in the art of the '238 and '342 patents thus would have understood Lilly's '843 patent to teach that the '843 patent inventors were aware of, and had tried, multiple purification methods, including "ion exchange chromatography," which includes anion exchange chromatography. Tr. 792:4-793:6 (Gerwick); Tr. 521:15-523:13 (Baker). A person of ordinary skill in the art would also have known that these methods failed to significantly improve the purity of daptomycin. Tr. 792:4-793:6 (Gerwick); Tr. 521:15-523:13 (Baker). Accordingly, a person of skill in the art would have been dissuaded from trying anion exchange chromatography, either as a single step or in multiple iterations, or any other form of chromatography to improve the purity of daptomycin above 93%. Tr. 792:19-794:8 (Gerwick).

95. Protein Purification is a general reference text describing various techniques and methods for separating and purifying proteins. *See* DTX-385; Tr. 794:17-795:17 (Gerwick). But daptomycin is a lipopeptide, not a protein, and Protein Purification does not discuss daptomycin or any other lipopeptide. Tr. 549:15-550:11 (Baker); Tr. 794:17-795:13 (Gerwick). In addition, the reference describes protein purification techniques in general terms and does not discuss specific conditions relevant for the purification of daptomycin. Tr. 550:8-11 (Baker).

96. Debono 1987 describes studies by Lilly scientists that were designed to determine the structure of the A21978C class of antibiotics, which includes daptomycin. *See* DTX-292; Tr. 795:18-797:5 (Gerwick). The paper does not describe the purification of daptomycin, but rather related compounds. *Id.* The paper does not disclose specific purification conditions, and it does not teach or suggest purifying daptomycin using micelle or aggregate formation. *Id.* Debono 1987 does not discuss whether the purified compositions contained endotoxins or saponins, and it does not include purity levels for any of its compositions. *Id.*

97. Lin discusses purification techniques used for the molecule surfactin, including ultrafiltration of surfactin micelles and aggregates. *See* DTX-345; Tr. 797:6-16 (Gerwick). Lin was considered by the Patent Office during the prosecution of the '238 and '342 patents. PTX-4; DTX-5; Tr. 797:9-12 (Gerwick). Surfactin differs from daptomycin in several key ways. Tr. 797:20-24 (Gerwick). First, "surfactin" refers to a collection of closely related molecules, while daptomycin is a single molecule. Tr. 798:4-799:19 (Gerwick). This is relevant to purification because one would want to design a process that would remove closely related molecules from daptomycin, whereas one would want to keep closely related molecules together with surfactin. Tr. 799:5-16 (Gerwick). Second, surfactin is approximately a third smaller than daptomycin, which would make some size-based separation methods less effective for surfactin. Tr. 799:17-800:3 (Gerwick). Third, the number and location of amino acids in surfactin and daptomycin is different. Tr. 800:4-18 (Gerwick); Tr. 550:24-551:6 (Baker). Because these amino acid differences affect the three-dimensional shapes of the molecules, they create differences in how the molecules will interact with purification systems. Tr. 800:4-18 (Gerwick). Finally, daptomycin contains both positive and negative charges at neutral pH, while surfactin contains only negative charges. Tr. 800:19-25 (Gerwick); Tr. 550:24-551:18 (Baker). This difference

allows use of different purification techniques for daptomycin that do not exist with surfactin, and also affects how daptomycin will behave in different pH conditions. Tr. 800:19-25 (Gerwick). Purification options that may work for surfactin, such as purification at high pH, cannot be used with daptomycin because the conditions may cause daptomycin to degrade. Tr. 553:19-22 (Baker). These significant chemical differences between daptomycin and surfactin make prior art concerning surfactin of limited value for achieving high purity daptomycin compositions. Tr. 801:22-802:8 (Gerwick). Moreover, these differences also make it difficult to infer that daptomycin will form micelles in a way that is useful for purification based on the teaching of Lin. Tr. 800:25-803:4 (Gerwick). As Hospira's expert admitted, the conditions under which different molecules will form micelles vary, and it is necessary to do experiments to determine whether a molecule will form micelles at all. Tr. 553:1-18 (Baker).

98. Lakey describes a series of experiments to determine how daptomycin kills bacterial cells. *See* DTX-333; Tr. 803:5-805:17 (Gerwick); Tr. 554:10-15 (Baker). It does not discuss the purification of daptomycin. Tr. 804:3-9 (Gerwick); Tr. 554:10-15, 555:4-8 (Baker). Lakey speculates that some of the results observed in one of its studies could "possibly [be] due to aggregation effects." DTX-333.3. From this observation, the authors conclude that "[i]n all the experiments described here we can assume that the lipopeptide is in monomer form. However, our ^{1}H NMR studies have shown that aggregation does occur at concentrations higher than 10^{-3} M." DTX-333.5. Lakey does not provide any detail about the conditions used in the experiment; it does not disclose micelle formation or disaggregation; and it does not teach or suggest using aggregation to purify daptomycin. Tr. 803:5-805:17 (Gerwick); Tr. 555:4-556:7 (Baker). Based on Lakey, a person of ordinary skill could not have predicted whether or under what conditions daptomycin would form micelles, or have had any reasonable expectation of

success that a purification method utilizing daptomycin aggregate or micelle formation would make production of high purity daptomycin compositions possible. Tr. 804:1-805:17 (Gerwick).

(b) Differences Between the Claimed Subject Matter and Prior Art

99. Claim 91 of the '238 patent is directed toward a purified daptomycin composition containing no more than 0.5% of each of the fourteen daptomycin related substances and obtained by a process comprising the step of forming a daptomycin aggregate. *See* PTX-4, 43:4-6. Lilly's '843 patent process produces daptomycin compositions that have at least six daptomycin related substances present in amounts greater than 0.5%. *See supra* ¶ 92. Because the prior art suggested it would not be possible to produce a daptomycin composition having less than 0.5% of some of the daptomycin related substances—particularly the anhydro-daptomycin and beta isomer impurities, and perhaps others—the claimed compositions would not have been obvious to a person of ordinary skill in the art. *See* Tr. 791:7-25, 805:18-806:10 (Gerwick). Furthermore, because no combination of Lilly's '843 patent, Protein Purification, Debono 1987, Lin, and Lakey suggests suitable methods of obtaining daptomycin compositions having less than 0.5% of each one of the daptomycin related substances, the claimed composition is not obvious. *See* Tr. 805:18-806:10 (Gerwick). The prior art does not teach or suggest purification of daptomycin using an aggregation step as claimed. Moreover, in light of the failure of chromatography methods as described in the '843 patent specification, a person of ordinary skill in the art would not have been motivated to subject the product of Lilly's '843 patent process to further chromatography to obtain a more pure composition, nor would that person have had a reasonable expectation of successfully improving daptomycin purity by doing so. *See id.*

100. Claim 98 of the '238 patent is directed toward daptomycin compositions of greater than or about 93% purity relative to the daptomycin related substances and prepared by method steps including forming of a daptomycin aggregate, separating the aggregate from low molecular

weight contaminants, changing the daptomycin aggregate into individual daptomycin molecules, and separating the individual daptomycin molecules from high molecular weight contaminants. *See* PTX-4, 43:7-30; Tr. 775:12-21 (Gerwick). As discussed above, unlike the prior art, the daptomycin compositions prepared according to the claimed process steps contain minimal levels of endotoxin, saponins, and some related substances. *See supra* ¶¶ 77-79. Because no combination of Lilly's '843 patent, Protein Purification, Debono 1987, Lin, and Lakey teaches or suggests methods of obtaining daptomycin compositions containing minimal levels of endotoxin, saponins, and these related substances, the claimed composition is not obvious. *See* Tr. 807:9-808:7 (Gerwick). Specifically, none of the prior art references teaches, suggests, or provides any reasonable expectation of success in obtaining high purity daptomycin compositions using a aggregation and size exclusion/ultrafiltration steps that remove both high and low molecular weight impurities to provide an improved composition as claimed. 807:22-808:7 (Gerwick).

101. Claim 187 of the '238 patent is directed toward daptomycin compositions of at least or about 97% purity relative to the daptomycin related substances and obtained from a lipopeptide aggregate comprising daptomycin. *See* PTX-4, 49:6-7; Tr. 808:8-16 (Gerwick). Because the daptomycin compositions of Lilly's '843 patent were at most 93% pure and the general belief in the field was that an equilibrium between daptomycin and its impurities would preclude the existence of a daptomycin composition of 97% purity, the claimed compositions would not have been obvious to a person of ordinary skill in the art. *See supra* ¶¶ 70, 80; Tr. 808:17-809:4 (Gerwick). Furthermore, because no combination of Lilly's '843 patent, Protein Purification, Debono 1987, Lin, and Lakey suggests suitable methods that would provide any reasonable expectation of success in obtaining daptomycin compositions having 97% purity, let alone a purification method including the use of a daptomycin aggregate as claimed, the claimed

composition is not obvious. *See* Tr. 809:5-810:12 (Gerwick).

102. Claim 23 of the '342 patent is directed toward pharmaceutical compositions of daptomycin having greater than 93% purity relative to the daptomycin related substances and less than 4% each of anhydro-daptomycin and beta isomer of daptomycin, prepared by process steps including anion exchange chromatography and filtration of a daptomycin aggregate comprising a daptomycin micelle. DTX-8, 39:1-7; Tr. 810:13-811:3 (Gerwick). Compositions made according to the claimed process steps contain minimal levels of saponins and some related substances, making these compositions different from daptomycin compositions that existed in the prior art. Tr. 811:4-18 (Gerwick). Example 10 of the '342 patent shows that the use of the anion exchange chromatography steps described in the '342 patent on a daptomycin composition produced by the '843 patent process reduces the number of daptomycin related substances from fourteen to one. DTX-8, 34:64-35:5; Tr. 811:12-18 (Gerwick); *cf.* Tr. 706:1-7 (Kelleher). Because no combination of Lilly's '843 patent, Protein Purification, Debono 1987, Lin, and Lakey teaches or suggests suitable methods of obtaining daptomycin compositions as claimed, claim 23 is not obvious. *See* Tr. 811:19-812:5 (Gerwick). In particular, none of the references teach or suggest purification using a daptomycin micelle, and Lilly's '843 patent teaches that anion exchange chromatography failed to improve daptomycin purity. Therefore, one skilled in the art would not have been motivated to attempt the recited combination of method steps to obtain an improved, highly pure daptomycin composition as claimed, nor would a person of ordinary skill in the art have had any reasonable expectation of success in doing so.

103. Claim 53 of the '342 patent is directed toward lyophilized powder pharmaceutical compositions containing daptomycin of about 94-96% purity relative to the daptomycin related substances and having less than 1% of the lactone hydrolysis product of daptomycin and less

than 4% each of anhydro daptomycin and beta isomer of daptomycin, prepared by a process including forming a daptomycin aggregate and converting the aggregate to individual daptomycin molecules, as well as anion exchange chromatography and/or hydrophobic interaction chromatography. DTX-8, 40:58-41:3; Tr. 812:6-17 (Gerwick). Compositions made according to the claimed process steps contain minimal levels of saponins and some related substances, making these compositions different from daptomycin compositions that existed in the prior art. *See supra* ¶¶ 77-79, 102; Tr. 812:18-813:2 (Gerwick). Because no combination of Lilly's '843 patent, Protein Purification, Debono 1987, Lin, and Lakey teaches or suggests suitable methods of obtaining, or provides a person of ordinary skill in the art with any reasonable expectation of success in achieving, the highly pure daptomycin compositions as claimed, claim 53 is not obvious. *See* Tr. 813:3-11 (Gerwick).

(c) Objective Indicia of Non-Obviousness

104. Cubist's discovery that daptomycin reversibly forms aggregates under certain conditions and that those conditions can be used to purify daptomycin from both low and high molecular weight impurities would have been surprising and unexpected to one of ordinary skill in the art at the time of the invention. Tr. 913:11-914:3 (Myerson); *see also* Tr. 706:19-707:7 (Kelleher). This supports the nonobviousness of the claimed inventions directed to daptomycin compositions purified using aggregates.

105. The yield of the daptomycin production methods used by Lilly in the 1980s and 1990s was, on average, about 2%. Tr. 925:10-22 (Myerson). A commercially viable pharmaceutical manufacturing process requires at least about 10% yield, and typically over 20%, or the cost of manufacturing the drug will be prohibitively expensive. Tr. 925:23-926:4 (Myerson). The method steps recited in the asserted claims filled the need for a new, commercially viable process of daptomycin production by allowing Cubist to achieve a yield of between 25% and 35%. Tr.

926:5-18 (Myerson); Tr. 713:16-19 (Kelleher).

106. The expense of purifying a drug substance generally represents about 40-60% of the cost of manufacturing. Tr. 922:19-923:1 (Myerson). Therefore, effective and efficient purification processes are important to the success of a new drug. Tr. 922:10-18 (Myerson). The process steps and resulting compositions recited in the asserted claims of the '238 and '342 patents fulfilled a long-felt need for an efficient and effective method to make highly pure daptomycin on a commercial scale, which supports the non-obviousness of the claimed inventions. Tr. 915:20-916:5 (Myerson).

3. Proposed Conclusions of Law Regarding Non-Obviousness

107. For the reasons explained above, *see supra* ¶¶ 91-103, Hospira has failed to establish by clear and convincing evidence that each of the asserted claims of the '238 and '342 patents would have been obvious in light of the prior art. Moreover, for the reasons explained above, *see supra* ¶¶ 104-106, objective indicia of non-obviousness, including unexpected results and long-felt but unmet need, show that the asserted claims of the '238 and '342 patents were not obvious.

D. Hospira's Derivation Defense Is Precluded and Without Merit

108. At trial, Hospira asserted, for the first time, that the '238 and '342 patents were invalid under 35 U.S.C. § 102(f) because the inventors derived the inventions from Lilly. Tr. 58:15-21 (Hospira Opening); 419:21-420:1 (Hospira Counsel). This defense was not raised in Hospira's answers, its preliminary invalidity contentions, its responses to Cubist's interrogatories regarding invalidity assertions, or its expert reports or depositions. *See, e.g.*, D.I. 8. Hospira also failed to raise this defense in its pretrial submissions. This defense is not included in Hospira's Statement of Contested Issues of Fact and Law, and there are no proposed findings or conclusions with respect to it in Hospira's Proposed Findings of Fact and Conclusions of Law. D.I. 109, Ex. 13. The prejudice to Cubist of this late disclosure is significant. Despite derivation being a question

of fact, *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1344 (Fed. Cir. 2003), Cubist was denied all opportunities to conduct discovery on this issue. Hospira should thus be prevented from asserting this defense.

109. Even if it were not precluded, Hospira's derivation defense fails. "Derivation requires a showing of both (1) prior conception of the invention by another and (2) communication of that conception to the patentee that is 'sufficient to enable [him] to construct and successfully operate the invention.'" *Int'l Rectifier Corp. v. IXYS Corp.*, 361 F.3d 1363, 1376 (Fed. Cir. 2004) (quoting *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1577 (Fed. Cir. 1997)). Hospira failed to adduce any evidence establishing that Lilly manufactured, conceived, or communicated to the Cubist inventors daptomycin compositions identical to those claimed in the '238 and '342 patents. Dr. Baker, Hospira's sole expert on the '238 and '342 patents, offered no opinion to support a derivation theory. Tr. 503:17-22 (Baker). Hospira did not present testimony concerning the '238 and '342 patents from any Lilly scientists, or even identify specifically who the Lilly inventors were or whom it alleges provided the source of the invention. Moreover, the sole trial witness with knowledge of the purification-related communications between Lilly and Cubist, Dr. Kelleher, testified only that Cubist received "binders of technical information" about Lilly's project and consulted with unnamed Lilly employees. Tr. 692:17-22 (Kelleher). Dr. Kelleher testified that, at the time of the invention, Cubist "had not received any information from Lilly regarding micelles." Tr. 707:24-708:2 (Kelleher). This falls far short of evidence "sufficient to enable [him] to construct and successfully operate the invention." *Int'l Rectifier*, 361 F.3d at 1376 (quoting *Gambro Lundia*, 110 F.3d at 1577). Thus, Hospira's derivation defense should be rejected.

IV. THE ASSERTED CLAIMS OF THE RE'071 PATENT ARE VALID

A. The Certificate of Correction Is Valid

110. The RE'071 patent, issued on April 18, 2006, is a reissue of the '226 patent. PTX-3. Asserted claims 18 and 26 of the RE'071 patent are directed to compositions of compounds generally referred to as "formula 1," "formula 2," and "formula 3." Tr. 144:17-20 (Ganem); PTX-3, 15:50-17:4, 20:26-22:45. The compounds represented by "formula 1" and "formula 2" are anhydro-daptomycin and the beta isomer of daptomycin, respectively. PTX-3, 8:37-44.

111. The RE'071 patent describes the third compound in three ways. First, the claims of the RE'071 patent describe the compound as an "A21978C cyclic peptide . . . wherein R^N is n-decanoyl." PTX-3, 15:50-17:4, 20:26-22:45. The specification refers to this specific compound by its Lilly-assigned codename, LY-146032. PTX-3, 7:41-60; Tr. 165:1-10, 166:11-13 (Ganem). Second, the specification of the RE'071 patent describes "A-21978C cyclic peptides" with reference to how they are made, *i.e.*, by fermentation. PTX-3, 7:41-60; Tr. 168:9-171:9 (Ganem); 815:18-817:10 (Gerwick). The specification explains that "A-21978C cyclic peptides . . . are prepared from the A-21978C antibiotics," which are "a group of closely related, acidic peptide antibiotics . . . described . . . in U.S. Pat. No. 4,208,403." PTX-3, 6:56-61. U.S. Patent No. 4,208,403, in turn, expressly describes the A-21978C antibiotics as being "produced by . . . fermentation of *Streptomyces roseosporus*." DTX-9, abstract. Similarly, the RE'071 patent refers to "an improved method of preparing the parent group of cyclic peptides [that is] described by [U.S. Patent No. 4,885,243]." PTX-3, 7:51-55; Tr. 815:10-816:15 (Gerwick). U.S. Patent No. 4,885,243 is directed to "[a]n improved process for producing A-21978C cyclic peptide derivatives" by using a new food "during the production stages of the fermentation." DTX-5, abstract. LY146032 is daptomycin. Tr. 165:6-7 (Ganem). Third, the RE'071 patent describes the compound of "formula 3" by a structure drawing that is labeled "formula 3." PTX-3, 7:1-60; Tr. 166:7-10 (Ganem). The "formula 3" structure drawing depicts daptomycin by showing how

its thirteen amino acid components are connected. Tr. 118:21-119:1 (Ganem). The amino acids are depicted by a three-letter code preceded by either "L-" or "D-", which describe how the atoms of the amino acid are arranged in three-dimensional space. Tr. 119:2-120:5 (Ganem). The "L-" form of an amino acid is the mirror image of the "D-" form and vice versa. Tr. 119:19-120:5 (Ganem). One of the amino acids in "formula 3" is asparagine, which is represented as "Asn." Tr. 119:2-120:5 (Ganem).

112. The application for the '226 patent, filed in 1987, showed the "formula 3" structure drawing as containing "L-Asn." *See, e.g.*, DTX-532.23. At that time, the scientific community understood this structure to represent the daptomycin fermentation product. Tr. 121:10-16 (Ganem). In 2005, however, Cubist researchers published a study (the "Miao paper") that refined the understanding of daptomycin's structure, using analytical techniques that were not available in 1987.[15] Tr. 178:1-7 (Ganem). The Miao paper concluded that daptomycin actually contains D-Asn, not L-Asn. DTX-359. Revisions of this nature occur "quite frequently" with molecules like daptomycin. Tr. 820:18-24 (Gerwick); *see also* Tr. 178:8-18 (Ganem).

113. Although the Miao paper corrected the assignment of stereochemistry for one amino acid in daptomycin, the nature and character of daptomycin itself did not change. All clinical trials that were conducted with daptomycin used the D-Asn compound. Tr. 156:16-25 (Ganem). The compound that the RE'071 patent refers to as LY146032 always contained D-Asn, Tr. 818:14-18 (Gerwick), and daptomycin produced using fermentation always had, and still always has, D-Asn. Tr. 171:7-24 (Ganem); Tr. 817:8-13 (Gerwick).

114. In light of this refined understanding of daptomycin's structure, Cubist filed a Request for Certificate of Correction for the RE'071 patent on October 18, 2007. DTX-96. The request

[15] V. Miao et al., *Daptomycin Biosynthesis in* S. roseosporus*: Cloning and Analysis of the Gene Cluster and Revision of Peptide Stereochemistry*, 151 Microbiology 1507 (2005) (DTX-359).

sought to change "L-Asn" to "D-Asn" in each "formula 3" structure diagram, including in the claims. *Id.* In the request, Cubist stated that "[t]he mistakes identified in the appended Form are . . . believed to be of a minor character, and therefore correctible by certificate of correction." *Id.* at 1. Cubist also attached the Miao paper to the request and stated that it "describes the discovery of this error." *Id.* at 1-2. The request also notes that Cubist's attorneys "contacted [the patent examiner] by telephone on October 2, 2007, to discuss this matter and determine whether a certificate of correction was appropriate in these circumstances. [The Examiner] confirmed in a later telephone call that same day that a Certificate of Correction appeared to be appropriate in these circumstances." *Id.* at 2. A certificate of correction issued for the RE'071 patent on Jan. 29, 2008 (the "Certificate of Correction"), making all of Cubist's requested changes. DTX-185.

115. Pursuant to 35 U.S.C. § 255, the Patent Office may "issue a certificate of correction" "[w]henever a mistake . . . of minor character . . . appears in a patent." A mistake that, if corrected, would broaden the scope of a claim cannot be a mistake of "minor character." *Superior Fireplace Co. v. Majestic Prods. Co.*, 270 F.3d 1358, 1375 (Fed. Cir. 2001). A certificate of correction may only be invalidated by clear and convincing evidence. *Id.* at 1367.

116. A person of ordinary skill in the art of the RE'071 patent would have a degree in chemistry, biochemistry, microbiology, or a complementary discipline relevant to the study and identification of drugs from natural origin, and have laboratory experience in the preparation, purification, analysis, and/or characterization of natural products for medicinal use. Tr. 814:22-815:6 (Gerwick).

117. Hospira failed to prove by clear and convincing evidence that the Certificate of Correction is invalid. As an initial matter, Hospira's legal analysis is flawed because it focuses on only one description of the claimed compound—the "formula 3" structure diagram—and fails

to address the claims' description of the compound as "an A21978C cyclic peptide." PTX-3, 16:44-46, 21:41-45. The term "A21978C cyclic peptide . . .wherein R^N is n-decanoyl" is not a term of art and does not have a generally accepted meaning, as Hospira's expert conceded. Tr. 167:23-168:2, 181:6-9 (Ganem). The specification is clear that "A21978C cyclic peptide" refers to a fermentation product, and fermentation has always produced daptomycin with D-Asn. *See supra* ¶ 113. Similarly, the specification is clear that "an A21978C cyclic peptide . . . wherein R^N is n-decanoyl" is LY146031, *i.e.*, daptomycin. *See supra* ¶ 111. Yet, despite clear Federal Circuit law that ambiguous claim terms "must be construed so as to be consistent with the specification, of which they are a part," *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 347 F.3d 1367, 1371 (Fed. Cir. 2003), Hospira's expert failed to consider the specification "at all" when offering his opinion about the scope of the uncorrected claims. Tr. 164:1-13 (Ganem). As Hospira's construction of the uncorrected claims is flawed, so too is its broadening analysis.

118. The Certificate of Correction did not broaden the scope of the asserted claims. The RE'071 patent describes the compound of "formula 3" in three ways. *See supra* ¶ 111. Two of these ways, LY146032 and as a fermentation product, consistently described a compound that had D-Asn—both before and after the Certificate of Correction. *See supra* ¶ 113. There is no dispute that at the time the patent application was filed, persons of ordinary skill understood the patent's third way of describing the compound of "formula 3," the structure diagram, to describe the same molecule as the other two descriptions. *See supra* ¶ 112. By correcting the "formula 3" structure diagram to be consistent with the findings of the Miao paper, the Certificate of Correction brought the structure diagram back into harmony with the other descriptions of the compound of "formula 3" in the patent—just as it had been when the patent application was filed in 1987. The correction did "not add to or change the nature of the disclosed inventions,"

Regents of Univ. of N.M. v. Knight, 321 F.3d 1111, 1122 (Fed. Cir. 2003). Accordingly, the Certificate of Correction did not broaden the claims and is valid.

B. The Corrected Claims Satisfy the Written Description Requirement

119. 35 U.S.C. § 112(a) requires a patentee to provide sufficient written description to allow a person of skill in the art to know that the inventor was in possession of the invention at the time of filing. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* "For claims to a chemical compound, an application satisfies the written description requirement when it details 'relevant identifying characteristics' such that the compound can be distinguished from other compounds." *Pfizer Inc. v. Teva Pharm. USA, Inc.*, No. 2012-1576, 2014 WL 463757, at *5 (Fed. Cir. Feb. 6, 2014) (quoting *In re Wallach,* 378 F.3d 1330, 1333, 1335 (Fed. Cir. 2004)). Written description "is a question of fact," *id.*, and the party asserting invalidity based on lack of written description bears the burden of demonstrating invalidity by clear and convincing evidence. *Id*.

120. The asserted claims of the RE'071 patent are not invalid for lack of written description. It is undisputed that a person of ordinary skill in the art reading the RE'071 patent in 1987 would understand that the inventors were in possession of the naturally occurring daptomycin molecule. *See* Tr. 186:13-187:6 (Ganem); Tr. 825:22-826:19 (Gerwick). Hospira contends that the claims are invalid because a person of skill would not have understood that the inventors possessed "daptomycin having the D-Asn configuration." Tr. 151:21-152:9 (Ganem). However, a person of skill, in light of the "relevant identifying characteristics" described in the specification—*i.e.*, the use of the Lilly code-word for daptomycin ("LY146032") and the reference to the "A21978C cyclic peptides," which described the invention as a fermentation product—would have

understood that the patent claimed the naturally occurring daptomycin molecule. *See supra* ¶ 118. Thus, the claims are supported by adequate written description.[16]

C. The Asserted Claims of the RE'071 Patent Are Not Invalid for Improper Recapture

121. The recapture rule prohibits a patentee from obtaining in reissue claims to subject matter that the patentee deliberately surrendered during the course of the original patent prosecution. *See Yoon Ja Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1322 (Fed. Cir. 2006). If the reissue claims are in all aspects narrower than those in the original patent, the recapture rule will not apply. *Id.* If the reissue claims are not narrower than those of the original application, "[t]he first step . . . is to determine whether and in what 'aspect' the reissued claims are broader than the patent claims." *In re Clement*, 131 F.3d 1464, 1468 (Fed. Cir. 1997). "The second step [examines] whether the broader aspects . . . relate to surrendered subject matter." *Id.* at 1468-69. Subject matter is not deemed "surrendered" absent an implicit admission that the prior art prohibited the original patent application from claiming that surrendered subject matter. *See Medtronic, Inc. v. Guidant Corp.*, 465 F.3d 1360, 1375-76 (Fed. Cir. 2006).

122. The asserted claims of the RE'071 patent are to a composition of three compounds: compounds of formula 1, formula 2, and formula 3. PTX-3, 15:50-17:4, 20:26-22:45. The claims, which are written with the inclusive "comprising" term,[17] require *each* of the three compounds to be present in the composition. In contrast, the canceled claim of the '226 patent

[16] At trial, Hospira did not present any evidence that the asserted claims of the '967, '689, '238 or '342 patents were invalid for lack of written description. *See* Tr. 382:13-383:4 (Ebert, Hospira Counsel); Tr. 500:17-19 (Baker). As a consequence, Cubist has not addressed any such argument in these proposed findings. In any event, these patents satisfy the written description requirement. As construed by the Court, the claims of those patents do not refer to daptomycin in terms of any specific stereochemistry. D.I. 59 at 1-3, n.1. Moreover, Hospira presented no evidence that persons of skill in the art would have questioned that the inventors were in possession of daptomycin, the clinically active antibiotic fermentation product.

[17] Claim 18 is illustrative: "An antibiotic composition *comprised of* a combination of a compound of formula 1, a compound of formula 2 and a compound of formula 3, or pharmaceutically acceptable salts thereof . . . ." PTX-3, 15:50-17:4 (emphasis added).

(claim 24[18]) was directed toward daptomycin "in substantially pure form." DTX-532.53. The canceled claim was silent as to the presence of compounds of formulas 1 and 2. *Id.* Accordingly, the asserted claims of the RE'071 patent are narrower than canceled claim 24 of the '226 patent, and the recapture rule does not apply.

123. Even if the scope of the asserted claims is not narrower than canceled claim 24 of the '226 patent, Hospira has failed to demonstrate by clear and convincing evidence that the patentees recaptured surrendered subject matter. Claim 24 of the '226 patent was not canceled to overcome a prior art rejection. During prosecution, the examiner rejected claim 24 under 35 U.S.C. § 112, ¶ 1 (written description). DTX-532.104. The applicants canceled claim 24 in response to this non-prior-art rejection. DTX-532.110. Thus, the subject matter of the canceled claim was not surrendered, and the recapture rule does not invalidate the asserted claims.

V. RELIEF[19]

124. Because Hospira has stipulated that its proposed generic daptomycin products will infringe the asserted claims and because those claims are not invalid, an order should be entered enjoining the FDA from approving Hospira's ANDA No. 202857 and NDA No. 203797 and enjoining Hospira from commercially manufacturing, using, offering for sale, or selling its proposed daptomycin products prior to the expiration of the asserted patents, including any associated extensions and exclusivities.

[18] Hospira argues that cancellation of claim 24 during prosecution of the '226 patent surrendered the subject matter of the asserted claims. D.I. 109, Ex. 13, ¶¶ 691-701. Hospira has not asserted that the RE'071 patent is invalid for improper recapture over any other canceled claims.

[19] Although Hospira's pretrial filings raised the issue of whether this case is exceptional under 35 U.S.C. § 285, *see* D.I. 109, Ex. 3, ¶ IV.A.3, no party has made a motion for fees. The fees issue is, at this point, premature. Regardless, particularly considering that Hospira has stipulated to infringement of all of the asserted claims, the assertion that this case is exceptional is meritless.

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April 4, 2014

CERTIFICATE OF SERVICE

I hereby certify that on April 4, 2014, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on April 4, 2014, upon the following in the manner indicated:

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